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PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

ORTHOPEDIC AND REHABILITATION DEVICES

ADVISORY PANEL MEETING

Monday, June 9, 1997

10:05 a.m.

Gaithersburg Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
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PARTICIPANTS

Barbara D. Boyan, Ph.D., Temporary Chairperson
Jodi H. Nashman, M.S., Executive Secretary

MEMBERS

Doris M. Holeman, Ph.D., Consumer Representative
Leela Rangaswamy, M.D.
Raymond Silkaitis, Ph.D., Industry Representative

VOTING CONSULTANTS

A. Seth Greenwald, D.Phil.
Roger M. Nelson, Ph.D.
Marcus P. Besser, Ph.D.
David L. Nelson, M.D.
Sally A. Rudicel, M.D.
Harry B. Skinner, M.D.

C O N T E N T S

P R O C E E D I N G S

MS. NASHMAN: Good morning, everybody. We are ready to begin this meeting of the Orthopedic and Rehabilitation Devices Panel.

My name is Jodi Nashman. I am a biomedical engineer, executive secretary of this panel, and a reviewer on the Orthopedic Devices Branch.

I would like to remind everyone that you are requested to sign in on the attendance sheets which are available at the tables by the doors. You may also pick up an agenda and information about today's meeting including how to find out about future meeting dates through the advisory panel phone line and also how to obtain meeting minutes or transcripts outside by the door.

I am going to now read two statements that are required to be read into the record.

First, is the deputization of temporary voting member statement. The second is the conflict of interest statement.

Pursuant to the authority granted under the Medical Devices Advisory Committee charter, dated October 27th, 1990, and as amended April 20th, 1995, I appoint the following people as voting members of the Orthopedic and Rehabilitation Devices Panel for the duration of the meeting

on June 9th and 10th, 1997: Marcus P. Besser, A. Seth Greenwald, David L. Nelson, Roger M. Nelson, Sally A. Rudicel, and Harry B. Skinner, M.D.

For the record, these people are Special Government Employees and are either a consultant to this panel or consultant or voting member of another panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review. They have reviewed the material to be considered at this meeting.

Also, because the position of panel chairman for the Orthopedic and Rehabilitation Devices Panel is currently vacant, I appoint Barbara D. Boyan, Ph.D., to act as a temporary chairman for the duration of the Orthopedic and Rehabilitation Devices Panel meeting on June 9th and 10th, 1997.

For the record, Dr. Boyan is a Special Government Employee and is a voting member of the Orthopedic and Rehabilitation Devices Panel. Dr. Boyan has undergone the customary conflict of interest review, she has reviewed the material to be considered at this meeting.

This is signed D. Bruce Burlington, M.D., the Director for the Center for Devices and Radiological Health, and it is dated 5-28-97.

The conflict of interest statement. The following

announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the Agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit Special Government Employees from participating in matters that could affect their or their employer's financial interests. However, the Agency has determined that participation of certain members and consultants, the need for whose service outweighs the potential conflict of interest involved is in the best interest of the Government.

Waivers have been granted for Dr. David Nelson and Dr. Harry Skinner for their interest in firms which could potentially be affected by the panel's discussions. The waivers permit these individuals to participate in all matters before the panel.

Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

Before turning the meeting over to Dr. Boyan, I would like to introduce our distinguished panel members who are generously giving their time to help the FDA in the

matters being discussed today, and other FDA staff seated at this table.

I will just start from my left. Dr. Doris Holeman is the Consumer Rep for the panel. Dr. Raymond Silkaitis is the Industry Rep for the panel. Both Dr. Holeman and Dr. Silkaitis are nonvoting members.

Dr. Roger M. Nelson, who is not to be confused with Dr. David L. Nelson; to my left is the Chairman, Barbara D. Boyan or Acting Chairman; myself, Jodi Nashman; to my right, Dr. Marcus Besser; temporarily missing in action is Dr. Leela Rangaswamy; Dr. Sally A. Rudicel, A. Seth Greenwald, and Dr. Harry Skinner.

Also seated at the table is the Division Director for the Division of General and Restorative Health, Dr. Celia Witten.

At this time, I would like to turn the meeting over to our chairperson, Dr. Barbara Boyan.

Welcome

DR. BOYAN: Good morning. My name is Dr. Barbara Boyan and I am the temporary chairperson acting for this meeting.

Today, the panel will be making recommendations to the Food and Drug Administration on three Class III pre-amendments premarket approval applications. I would

like to note for the record that the voting members present constitute a quorum as required by 21 CFR Part 14.

Before getting started on the PMA applications, I would like to turn the meeting over to Jim Dillard, Deputy Director, Division of General and Restorative Devices, who will describe to the panel happenings in the division since the last panel meeting.

After Jim's presentation, Mark Melkerson, Branch Chief of the Orthopedics Branch, and Tracey Bourke, Medical Officer of the Rehabilitation Devices Branch, will present branch updates.

Jim.

Orthopedics & Rehabilitation Branch Devices:

Progress Since Last Panel Meeting

MR. DILLARD: Thank you, Dr. Boyan.

First of all, I would like to just begin by welcoming you all to Maryland. We appreciate that you have come and gladly donated your time to help us in the three PMAs that will be before us both today and tomorrow, so again welcome and thank you very much and Dr. Boyan for chairing the meeting. We appreciate it.

What I would like to do, to begin with, is just give you a brief update from the last time the Orthopedic and Rehabilitative Panel met and the happenings from that

time, and then, as Dr. Boyan mentioned, turn it over to Mark Melkerson and Tracey Bourke to give an update of their branch activities, and then what I would like to do is spend a few minutes to try to let the panel know, as well as the audience, about Class III pre-amendments devices of which the three products that we are going to be looking at over the next three days constitute that classification.

To begin with, the last time the Orthopedic and Rehabilitation Devices Panel met, it was actually a split meeting. The first day the panel was together to discuss Carticel from Genzyme and there was as full-day discussion, as well as some discussion and updates about what is happening in terms of tissue regulation at the Agency.

What I would to mention is that at that point in time, the Center for Biologics Evaluation and Research was utilizing our panel for your expertise during that day of deliberation. Currently, the Center for Biologics continues to work with the sponsor of Carticel in moving forward on activity for a final decision. To this point, to the best of my knowledge, there has not been a final decision on the product.

The second day was devoted to bone void fillers, which was actually something that the Division of General and Restorative Devices has been interested in, and what we

took from your input at that panel meeting is to work with various manufacturers as we move forward to try to determine what sorts of clinical trials and what sort of endpoints, as well as pre-clinical information, is necessary for us to be looking at as we are looking at new bone void filling materials. I think what that is going to be is the beginning of maybe at least one, if not two more, interactions with you as panel members as we move forward to clarify our direction in bone void fillers in various portions of the body.

At this point, I guess then that is really the update that I have from that two-panel meeting, and I will turn it over now to Mark Melkerson, and he is going to talk a little bit about some of the programs that are going on in the Orthopedic Devices Branch.

Mark.

Branch Update: Orthopedic Devices Branch

MR. MELKERSON: Good morning. My name is Mark Melkerson. I am the Branch Chief of the Orthopedic Devices Branch.

[Slide.]

Before we get started with the updates, I would like to go through some of our staff changes. I will start with Janine Morris. Even though she is on the second side,

she is our newest member to the Orthopedic Branch. Janine, would you like to stand up for a second. This is my chance to embarrass people once in a while.

Next to her is Samie Niver. Peter Allen. Our consumer safety technician, Michael Courtney. Erin Keith, who will be presenting one of the PMAs tomorrow. Aric Kaiser. Next to him is Paul Williams.

Sitting in the front row, who is not on our staff, but will be presenting the clinical data for all three PMAs, Dr. Stephen Nightingale. In the front row we have Hany Demian. On the far side, who will be flipping slides, John Goode.

[Slide.]

As far as updates from our PMA approvals, we brought the Sulzer Orthopedics, at that point in time it was the Intermedix Orthopedics, Natural Knee. That PMA has now been approved. One PMA that did not come before the panel, but was approved recently, was the DePuy Bone Cement.

[Slide.]

Guidance documents for '97. We have completed two and they were official in April 1997. The January date was when they were initially draft, and by the time they went through their formal approval process, it was April 8th, I believe, of 1997.

[Slide.]

One new guidance document that will be coming out soon -- and that came through some assistance of the AAOS Device Forum, as well as HIMA and the OZMA task groups was redrafting the polyethylene guidance. FDA plans to convert it into its format and use that as a final guidance.

[Slide.]

In terms of Class III pre-amendments devices, similar to the three you will be reviewing at this panel, there will be calls for PMAs for 515(b)'s for a metal on metal. Currently, that is pending. The resurfacing component -- and resurfacing is where you leave the femoral head intact and do not resect the neck -- was also going forward as a 515(b) or call for PMA.

[Slide.]

For informational purposes, August of 1997, we have two products that will be due for their 515(i)'s, and that is a call for information. The semi-constrained shoulders, which is currently being worked on, are the reclassification efforts from the American Academy of Orthopedic Surgeons Device Forum, and also the constrained elbows, again under reclassification efforts from the AAOS Device Forum.

[Slide.]

Guidance documents. As I mentioned earlier, we have been working on the ultra-high molecular-weight polyethylene. We have completed the external fixator and IM rods. Other ones that are currently being worked on are the porous coated plasma sprays, and clinical study designs and outcomes. It is just being initiated with the assistance of the AAOS Device Forum.

Reclassification efforts that the Device Forum has been working along with FDA. The Device Forum, for those that aren't aware of it, consists of the Orthopedic Research Society, American Academy of Orthopedic Surgeons, OZMA, and HIMA representatives, and invited guests of the FDA and ASTM.

Reclassification efforts. Again, total knees for uncemented use, constrained shoulders is currently the second in line, and then as priorities we have the constrained elbows, constrained hips, which you are looking at today under PMA, Patellofemoral knees, and bone cements.

[Slide.]

The Device Forum is also helping set priorities and participating in ASTM Standards activities and symposia. They were very beneficial in the last one, which was for spinal implants, as well as for titanium. The upcoming ones are alternative bearing surfaces and performance standards.

Developing educational programs along with the Device Forum. We are dealing with tissue regulations, custom device issues, and educational programs for IRB, clinicians, and investigators, also accessing FDA information.

[Slide.]

One of our more successful pilot programs which the Orthopedic Branch was responsible for was the real-time PMA Supplement Review Program. Under this program we have been dealing with labeling changes, design changes not requiring clinical data, changes standardized for sterilization from one method to another where you are going from ETO to gamma, or changes in your packaging.

Right now the goal for the office is to review these PMA supplements in a total of 30 days from date of receipt.

[Slide.]

Again, things that aren't reviewed under this program: new indications for use, designs, or materials, in other words, things that may be going to the panel for input; novel methods or changes in standardized. An example of this would be gas plasma spray sterilization methods which aren't standardized as of yet.

[Slide.]

Three types of reviews are possible right now within that 30-day goal period that we were talking about earlier: One where you just act directly with the reviewer, and it would go through a normal review cycle, branch chief signing off and then the division director; a telephone conference where you have identified the major concerns from the PMA supplement that is submitted to us; and then, of course, the other alternative is face-to-face meetings.

[Slide.]

We have another interactive pilot program in Orthopedics. It was initiated in Dr. Witten's behalf along with another division. It is scheduled to last about six months to a year.

[Slide.]

The goals: provide feedback to the sponsors in an earlier and more direct fashion, in other words, as we complete something that can be handled prior to the review cycle, please do so; if not, identify the major issues or concerns sooner to the manufacturer, so they know where we are in the review cycle; and then, of course, reduce the overall review times to cut down on things going over 180 days.

[Slide.]

Another pilot program that the Orthopedics Branch

is involved in is the Canadian/U.S. Partnering Program. It was initiated in October of last year. It again involves Orthopedics and now also ENT or Ears, Nose, and Throat. It is scheduled to last two years with an assessment again this October.

[Slide.]

The goals of this program are to learn about each other's review process; identify each country's more efficient says to review things and hopefully streamline our own; share perspectives on public health priorities and enhance priority setting by both groups.

[Slide.]

Gains in experience. While the Canadians are instituting a new review system, their regulations are currently awaiting signature. Being as we are also facing potential action as far as regulation reform, we are very curious to see what they have done in their program, and also build confidence between decisions in countries which may lead to international harmonization.

[Slide.]

Again, right now we are sharing and discussing procedures for reviewing documents. We deal with 510(k)'s, they deal with a Title V. Exchange with documents and reviews of particular scientific interest. In other words,

right now we are able to discuss design differences in others, how did you handle a particular technology, and also parallel reviews for similar or identical devices, but that requires a manufacturer to sign a release, so we can exchange both memos and technical information.

[Slide.]

This is kind of my sales pitch. We are actively trying to recruit sponsors to participate in the parallel reviews both under 510(k)'s, IDEs, and PMAs. Currently, we are sharing the clinical expertise from the Health Protection Branch of the Canadians while they are using our engineering staff, and we are both have a very large interest in guidance document development to cut down review times.

[Slide.]

International harmonization is another area which we have been tasked are the Orthopedics group. We are currently working on a Hip notebook, which basically assembles all the regulatory requirements from each country. We are to compare the similarities and differences and see if we can come up with a set that everybody can live with, and again, hips were seen as being something that everybody had a chance at.

[Slide.]

One thing that keeps coming up. Manufacturers have asked where do we go in terms of developing new technologies and still be within the regulations, and we are basically looking at a way to look at coming in earlier, having the manufacturers come with pre-IDE or pre-PMAs, or in that case, even pre-510(k) submissions to identify what questions need to be asked before making a submission.

[Slide.]

Product development options. Keep in mind that you can deal with feasibility studies, usually one site, 10 to 15 patients per site, where you are looking at developing a new device, looking at surgical instrumentation, tweaking and trying to get your surgical technique down.

A pilot study is another option that is available to manufacturers. It usually can be multiple sites used to train the investigators for investigation, usually three to five patients per site.

[Slide.]

And the last one. Pivotal studies which everybody is familiar with, which are your multi-center studies used to collect safety and effectiveness information.

We brought these up just to make sure the public is aware, and also manufacturers and clinicians, that there are alternative ways to bring products to market.

That concludes my presentation. I will turn it over to Tracey Bourke.

Branch Update: Rehabilitation Devices Branch

DR. BOURKE: Good morning. I am Dr. Tracey Bourke. I am a member of the Restorative Devices Branch also known as the Rehabilitative Devices Branch, and I will be giving a very brief branch update.

[Slide.]

I don't see any of the branch members here to introduce, but the current staff of the Restorative Devices Branch includes: Branch Chief Marie Schroeder, Dr. Bernard Berne, Dr. Christian Bowsher, Kirby Cooper, Robert DeLuca, Elmer Einberg, Steve Hinckley, Dr. Kevin Lee, Nadine Sloan, Dr. Angel Torres-Cabassa, and me. I am not a medical officer, I am a veterinarian, and I am also presently the branch's team leader.

[Slide.]

Secondly, Fidia Pharmaceutical Corporation's PMA for its device Hyalgan was reviewed by the panel on November 21st, 1996. The panel recommended PMA be approvable. As of May 28th, 1997, the PMA was approved.

Hyalgan is a viscous solution of purified natural sodium hyaluronate in buffered physiological sodium chloride. It is indicated for the treatment of pain and

osteoarthritis of the knee in patients who have failed to respond adequately to conservative nonpharmacological therapy and to simple analgesics.

[Slide.]

Lastly, the Bone Growth Stimulator Working Group, comprised of personnel from different FDA offices, met with industry representatives on May 13th, 1997, to discuss several issues, some of which were pre-market and post-market in nature.

Among the pre-market concerns were the following. A nonunion is currently defined for the purposes of a study as when a minimum of nine months has elapsed since the injury and the fracture site shows no visibly progressive signs of healing for a minimum of three months. No change in the fracture calix.

FDA wishes to keep this current definition only for study purposes in order to guarantee consistency and so that data can be interpreted. For clinical purposes, the clinician should handle the definition.

There is inappropriate marketing, that is, without approval, custom use claims and major device changes are made that can impact on performance and effect. Among the postmarket concerns were the following. The labeling and promotion sometimes include mechanism of action claims

without supportive data, when the device affects efficacy and safety and inadequate and unsupported comparisons between various devices with different exposure times to demonstrate superiority in terms of efficacy.

In the labeling, success/failure rates are often reported inconsistently or without prior approval. Examples of these include PMA data, postmarket data at two or four years, registry data, or only the best data of the three.

The FDA is still in the process of getting written industry comments on all issues discussed at the meeting which will be combined with FDA's comments in a future draft position paper. Prior to obtaining signoff from the offices of Device Evaluation and of Compliance, the draft position paper will be submitted to the panel for feedback.

This concludes my very, very brief update.

DR. BOYAN: Thank you.

Now, what we are going to do today, which is to discuss 515(b) Class III preamendments PMAs, is a little bit different than the PMAs generally brought before this panel.

At this time, I would like to reintroduce Jim Dillard who will describe this type of PMA application.

Introduction to 515(b) Class III Preamendments PMAs

MR. DILLARD: Thank you again, Dr. Boyan.

[Slide.]

I would like to just begin, I would like to give about eight or nine overheads and talk for about 15 minutes about the type of product that we are talking about, because I believe this is the first time that this panel has seen a preamendments Class III product brought before them for their consideration.

[Slide.]

I would like to just run through, give a little background and history about preamendments Class III devices, a couple of examples, talk about valid scientific evidence in the context of novel PMAs versus Class III preamendments PMAs, talk about a few new approaches that a reengineering effort inside the Center for Devices and Radiological Health is considering that does affect this area of product, and then conclude very briefly with a summary.

[Slide.]

Before I get started, there is one point I wanted to make just from the standpoint of this presentation, is that in this case, we will be asking for you, as the panel, to certainly give us a recommendation on approvability or not approvability of these PMAs based on the evidence before you, but it is equally as crucial from out standpoint for these products that have been on the market to get your

comments on labeling as it affects the use of the product, as well the indications and any other input that you might have regarding how the product might in the future be marketed.

In 1976, the Amendments, the original Classification panels were put together to give recommendations to the Agency about where to place products, either Class I, Class II, or Class III.

As you will remember, Class I products have general controls that govern the risk of the products. Class II products back in 1976 also had performance standards at the time, and then Class III products required a PMA.

At the time of the Classification panels, there was 141 devices that, not only this panel, but other panels decided the risk could not be controlled adequately with general controls and performance standards, and so they gave the recommendation that in the future, you ought to call for PMAs on the products.

SMDA 90 brought up the point that FDA had not worked very quickly to move forward in any of these areas, and so mandated that we actually do something with the existing 141 Class III devices.

One of the strategies that we moved forward on is

-- and I will jump to the bottom to begin with -- call for information through 515(i) part of the statute, to ask manufacturers to submit information on their existing product, so that we could move forward either with a reclassification effort or a call for PMA.

From the standpoint of a reclassification effort, all the Class III products could either be down-classified to Class II or Class I. There is nothing by statute that mandates that you have to go from III to II, it could be III to I.

The other option is to call for PMA through 515(b). Through a 515(b) PMA, these are the three products that you will be looking at over the next couple days, and one of the crux points that I think you need to realize is that FDA has to act in 180 days on these PMA, and we have two decisions that we have to make - either the product is approved and it stays on the market, or the product is not approved and it comes off the market, which is a little bit different than novel PMAs.

One of the ideas that we are certainly always tossing around from the standpoint of reclassification and one of the changes from performance standards was we have got special controls and SMDA 90. It broadened the scope of what we were utilizing for performance standards to special

controls, things like labeling controls, the use of existing other industry standards and guidance documents, just to name a few.

[Slide.]

In April of 1994, the Office of Device Evaluation put together a strategy for 117 of these products, 42 of these we categorized as Group 3 products that we at the time already believed that we were going to be calling for PMAs on these, some of which we have published proposed and final rules for PMA submission, some of which are currently in the proposal process and are continuing to move forward. I think Mark mentioned a few, metal-on-metal is one, and resurfacing arthroplasty is another one that is in that category.

There are 31 Group 2 devices that we felt in that 1994 strategy were probably good candidates already for reclassification. We called for information under 515(i) and still believe that there is a number of them that possibly could be reclassified.

The final Group 1 devices, originally, there were 44 proposed to call for PMA, and these were products that the Agency felt had either fallen into disuse or had fallen into minimal use, and so we called in a mass effort for PMAs to be submitted.

The final 515(b) rule to call for the PMAs was published September 27th, 1996, and it was for 41 devices. There was actually three classes of devices that sponsors came forth and said, no, we are not a disuse type product, we continue to want to market this product, so they were removed from the final rule.

The three products again that you are going to be looking at over the next couple days were in that category where the Agency thought there was disuse or minimal use, and we have come to find out that there are at least three manufacturers who are interested in marketing a few of those products, and I will go into those a little bit more in the next slide.

[Slide.]

Just by way of example, I put the first one from the final rule in the orthopedics area, the ankle joint metal/polymer non-constrained cemented prosthesis, but the three that are more appropriate for the next two days with the panel meetings, I have lumped into three classification categories for the finger joint and four for the hip joint.

These are the most appropriate ones that you are going to be considering and actually where the PMAs have come in. They have been covered under these product areas.

All three PMAs again were received in the

orthopedics product area. There were other products that were called in that disuse call for PMA, but none others were received in any of the other product areas.

[Slide.]

Valid scientific evidence. You have seen this before. Everybody in the audience I think is aware of it, too. It is in 21 CFR 860.7. Valid scientific evidence as defined in the Code of Federal Regulations ranges from well-controlled study to reports of significant human clinical experience with a marketed device.

I put this up for your information because I think it is going to be useful when we start talking about some of the potential differences between novel type PMA products and marketed Class III products.

[Slide.]

Novel PMA Class III products are the type that you, as the panel, are very used to seeing. We bring these before you because they are first of a kind, and by certainly our policy and by regulation, we bring these PMAs before you for your input.

You are very used to see well or partially controlled studies in these type of applications, and they are not obviously a currently marketed device. Many times and this panel has had open discussions about follow-up

times, two years, five years, 10 years. Much of the information on most of the PMAs you have looked at recently have had a two-year follow-up time frame.

Most of those PMAs have extensive statistical analyses and, of course, they have no MDR information because they are not a marketed product. MDR information is the medical device reporting system of adverse events that we use at the Food and Drug Administration.

Marketed Class III products, though, are much different. These products have been on the market. They were either a preamendments device that existed before May 28th, 1976, or they were a product that was cleared through the 510(k) process and found substantially equivalent to an already existing preamendments device, albeit when it went through that 510(k) process, it did get a Class III designation, but nonetheless, it was cleared through that process.

These marketed Class III products, since Congress has told us we need to either call for PMA or reclassify them, calling for PMA leaves us in an interesting situation because many of these products have been on the market, but they may not have, in a prospective fashion, had well-controlled or partially-controlled information. They very well may have, but the gamut of scientific information

that you may see in this product is probably a lot more diverse than what you would see with a novel PMA device.

So well controlled all the way down to -- not down to -- but including significant human experience with a marketed device are going to constitute valid scientific evidence, and should not be underplayed.

Much of this information may look very similar to what you see in some of your other activities as experts in your field looking at literature information, peer reviewing articles. Much of the information comes from peer review and nonpeer reviewed articles

There may be lesser statistical analysis. There may not be any statistical analysis. It could again range the gamut.

There is -- and again we ought to remember -- there is 20-plus years marketing history with this classification of product, but there may not be 20-plus years with the individual products that you will be looking at.

The likelihood, though, with some of these products of having a longer follow-up time is good. Many of these products have been on the market in general in the Class III categories and I think you should factor that in, in terms of marketing experience and the types of follow-up

times that might be gained, and then there is an MDR history which will be something that the review staff from the FDA will also talk about of the adverse events or lack of adverse events associated with the product. Again, both scenarios constitute valid scientific evidence.

[Slide.]

I just want to talk about a few of the new initiatives. We have a full-scale reengineering effort currently underway at the Center, one of which is dealing with all the Class III preamendments products, and I have been involved with that effort very closely.

One of the things we have looked at comes from many of our discussions in focus group situations with panel members and with other experts outside of the Agency, and one of the things we continue to hear is please use the panel earlier, please get us involved in study design, please get us involved before all the data has already been collected and we have had no input, and I think we are trying to take that to heart.

So you may find that in the future, we will be utilizing you in an open forum situation much earlier in the review process and maybe even most appropriately to help us set criteria in areas that would be very generic across a product category type or novel technology type.

I also see some usefulness for setting that criteria during the time frame when we call for PMAs to, before we go final with a call for PMAs under Section 515(b), that you could be very beneficial to us in taking a look at current state-of-the-art and whether or not additional information may be appropriate, so you may see us coming to you more often.

There is also a fairly large effort that we are working on to look at 50 to 60 of those Class III preamendments devices which appear to be appropriate for a reclassification effort. We have been through in the past mass reclassification efforts, down-classifying a number of Class II products to Class I, and then further exempting those products. We can foresee an effort, such as that, down-classifying a mass or a group of products from Class III to Class II, and we will be looking at some new ideas of special controls and utilizing, hopefully, more broadly the concept of special controls.

We also see as we have been working through our effort another smaller group of products that may have also fallen into disuse that we may be moving forward on.

[Slide.]

So just by way of summary, I hope I have given you a little bit of information about where these products come

from -- they are much different from the types of products that you have seen -- and also give you a little bit of appreciation of valid scientific evidence and how that might be applied in some of these circumstances.

I hope, and I would certainly welcome feedback at any point in time about any of the new approaches that we might be moving forward on, to finish up the effort of either downclassifying or calling for PMAs for all the remaining Class III products. Hopefully, that gives you a little bit of information about where at least the Agency is heading on this initiative.

If there is any questions, I would be happy to field them at this time, Dr. Boyan.

DR. BOYAN: I was going to do exactly that and open up your presentation to questions or comments from the panel.

Are there any questions or comments from the panel?

I will take the lead and state that I am pleased that you are considering using the panel earlier in the process. One of the things that had occurred to me as we reviewed these is that times have changed and new knowledge has come to the fore, and where certain preclinical tests may have been appropriate or have been considered

state-of-the-art 20 years when the 510(k) applications were made, more information is now available and that you might structure, not to penalize these individuals who clearly have a substantial amount of human data, but in future, to take the messages, the lessons we are learning from these re-reviews of existing devices and put them into PMA expectations or preclinical information.

A lot of what we have learned that happened clinically was predicted by preclinical data that the studies may have been planned with a little bit more rationale to them.

MR. DILLARD: Thank you. I appreciate that.

DR. BOYAN: Dr. Rangaswamy.

DR. RANGASWAMY: I guess in keeping with the same comments that Dr. Boyan made, I know you have a time limit of 180 days or 30 days earlier is what Mark had said. If you really want to do justice to looking at old data, which is unfortunately often very poorly done and published, then, one needs to sort of at least identify some kind of protocol that the sponsors of a particular product can use as guidelines in terms of when they want to do a retrieval of their own patients even if they didn't bring them all in, there should be a way of being able to get data to see where they are at this point in time, which I think will make it a

stronger study.

MR. DILLARD: Thank you again. We will take both of those to heart. I appreciate it.

DR. BOYAN: Any additional comments?

[No response.]

DR. BOYAN: Hearing no additional discussion, I would like to thank you very much, Mr. Dillard, and I will have us break for lunch.

We will reconvene at 12:30 for an open public hearing.

Thank you.

[Whereupon, at 10:45 a.m., the proceedings were recessed, to be resumed at 12:30 p.m.]

AFTERNOON PROCEEDINGS

[12:33 p.m.]

MS. NASHMAN: If we could all sit down, please. I think we are now ready to begin the afternoon session of this panel meeting. I will turn the floor back over to Dr. Barbara Boyan.

OPEN PUBLIC HEARING

DR. BOYAN: Thank you. We are now going to proceed with the open public hearing session of the meeting. I would ask at this time that all persons addressing the panel come forward and speak clearly into the microphone as the transcriptionist is dependent on this means of providing an accurate record of the meeting.

We are requesting that all persons making statements during the open public hearing of the meeting disclose whether they have financial interests in any medical device company. Before making your presentation to the panel, in addition to stating your name and affiliation, please state the nature of your financial interests, if any.

If there anybody that is wishing to address the panel?

[No response.]

DR. BOYAN: Okay. Since there are no requests to speak at the open public hearing, we are now going to

proceed to the open committee discussion, and the discussion of the first PMA being presented before the panel, Avanta Orthopaedics Braun-Cutter Trapezio-Metacarpal Prosthesis.

I would like to remind the public observers at this meeting that while this portion of the meeting is open to public observation, public attendees may not participate except at the specific request of the panel.

We are now ready to begin with the sponsor's presentation. I would like to ask that each speaker state his or her name and affiliation to the firm before beginning the presentation.

Would the sponsor like to begin their presentation?

Avanta Orthopaedics Braun-Cutter

Trapezio-Metacarpal Prosthesis

Sponsor Presentation

MS. FOCHT: I am Louise Focht, Vice President of Operations and Research and Development for Avanta Orthopaedics.

[Slide.]

I am presenting today the PMA application for Avanta Orthopaedics Trapezio-Metacarpal Prosthesis. This device was originally known as the Braun-Cutter

Trapezio-Metacarpal Prosthesis.

[Slide.]

To give you a little bit of background on our organization, we have a long history with small joint implants for the hand and foot, originally beginning in 1980 with Cutter Laboratories. The Cutter Laboratories in 1980 was sold to Sutter Biomedical, which was in 1985 sold to Smith Laboratories. In 1988, the name was changed to Sutter Corporation and known as Sutter Corporation while it was owned Columbia/HCA purchased in 1990.

In 1991, two divisions of Sutter Corporation were formed, Small Joint Orthopedics Division, whose mission was to address small joints for the hand and foot, and there was a home rehab organization, which was primarily CPM and Orthopedic Rehab Equipment.

In 1995, Columbia sold the Small Joint Orthopedics Division which formed as Avanta Orthopaedics. In 1996, we are registered under ISO 9001.

[Slide.]

Avanta Orthopaedics designs, manufactures, and markets products for reconstructive surgery of the upper extremity. We participate in a global marketplace. Our mission is to provide cost-effective quality orthopedic products and services that enhance patient outcomes and

facilitate the clinical practice.

We are an organization of 12 employees and we see our primary mission as providing products for the hand specialty.

[Slide.]

Function of the thumb. The thumb performs 40 percent of the hand function as reported by Burton in 1973. Thumb carpometacarpal arthritis is a common cause of loss of that thumb function, particularly in women over age 45.

[Slide.]

Techniques which are currently available for the treatment of the carpometacarpal joint of the thumb include conservative treatment, which may include rest, activity modification, splinting, antiinflammatory medication, physical therapy, and steroid injections.

Alternative surgical treatments include fusion, interposition arthroplasties using tendon or silicone joint spacers, and total joint arthroplasties using various ball and socket joint designs.

[Slide.]

Cooney in 1987 reported that since 1973, four different types of total joint arthroplasties have been used for thumb reconstruction. This included two products distributed by Howmedica, the Lewis TMC, and the de la

Caffiniere, the Braun-Cutter originally distributed by Cutter Labs, and now Avanta Orthopaedics, and the Mayo by DePuy.

Devices are marketed worldwide and we are unaware of any country which has withdrawn any of these products for any reason related to safety or effectiveness of the device.

[Slide.]

In 1974, Dr. Braun made a custom total joint replacement for a patient being treated for a gunshot wound, and this initiated a study to develop a total joint replacement for the treatment of the trapeziometacarpal joint.

In January of 1979, that product was cleared to market through the 510(k) process and was known as the Braun-Cutter Trapeziometacarpal Prosthesis.

In December of 1996, Avanta Orthopaedics filed a PMA application which was required to continue to market and distribute the Braun-Cutter TMC joint.

[Slide.]

The device is constrained because it prevents dislocation of the prosthesis in one or more anatomic planes and consists of components which provide across the joint linkage.

Both components are intended to articulate on each

other allowing for approximately plus or minus 45 degrees of motion from the neutral position. The articular surfaces prevent dislocation of the joint through captivation by a ball and socket.

[Slide.]

The materials the device is made of are industry standard materials consisting of titanium alloy and ultra-high molecular-weight polyethylene. This is the device. The metacarpal stem is titanium and the trapezial side is the ultra-high molecular-weight polyethylene.

[Slide.]

Surgical indications for the trapeziometacarpal prosthesis in adult patients include -- and these are taken from the literature primarily -- and include: degenerative or inflammatory joint disease of the trapezial metacarpal joint, degenerative basal joint arthritis, dislocation or subluxation of the trapezial metacarpal joint, posttraumatic arthritis, osteoarthritis, rheumatoid arthritis, ankylosis of the joint, failed joint replacement, failed silicone implant arthroplasty, and painful carpometacarpal joints with limitation of motion.

[Slide.]

Contraindications include: psychologically unsuitable patients, patients with skin, bone, circulatory,

and neurological deficiencies, non-functioning and surgically irreparable musculotendinous system, infection, growing patients with open epiphyses, patients with extremely high levels of activity, and triscaphi arthritis.

[Slide.]

Clinical data specifically regarding the Braun prosthesis was published on three occasions by Dr. Braun: Journal of Hand Surgery in 1982, Clinical Orthopedics in 1985, and Seminars in Arthroplasty in 1991.

[Slide.]

In 1982, Dr. Braun reported on 29 patients which had been followed from a range from 1 to 7 years; 22 patients achieved full range of motion, which was also pain free; 26 patients achieved good range of motion; 3 were reported to be loosened at the cement bone interface, 2 of which were the result of direct trauma; 2 had revisions and appeared to be doing well at that time; 1 dislocation which occurred 5 years post-op due to direct trauma in a fall.

[Slide.]

In 1985, Dr. Braun reported on 50 subjects followed for 6 months to 10 years. Full range of motion was achieved in 26 osteoarthritic patients; 12 patients with rheumatoid arthritis had associated problems which made comparison to the other groups difficult; 3 patients were

treated by a total joint arthroplasty after fusion; 2 patients with lupus showed no complications.

[Slide.]

The complication rate was reported to be less than 10 percent; 5 patients showed clinical or radiographic evidence of loosening, 4 were revised and 1 was followed. Tendonitis had also been clinically significant in 6 subjects.

[Slide.]

In 1991, Dr. Braun reported on 80 patients followed for more than 10 years. There were no implant fractures, no evidence of excessive wear. There was some deformation of the polyethylene noted. There were no infections, no unstable articular components.

[Slide.]

Primary complications reported were less than 10 percent. Loosening of the trapezium component in the cemented cases was noted. Metacarpal subsidence in the uncemented cases was noted; 5 uncemented metacarpals showed evidence of subsidence, 3 were revised, 2 at that point in time were planned to be revised, and 7 uncemented metacarpals showed no subsidence.

Two fractured trapeziums were treated with a titanium spacer which was made on a custom basis.

Dr. Braun predicted that approximately 10 percent of the cemented cases would loosen at some time in the future due to aging of the patients.

His conclusions were that the procedure was safe and reliable.

[Slide.]

The advantages of using a joint in the treatment of the basal thumb joint are that you can obtain immediate joint mobility, the range of motion is good, pain relief may be achieved, minimal bone resection is required, there is a minimal need for host healing response, and there is no major ligament reconstruction requirements of the procedure.

[Slide.]

In cases where revision is required, the components may be removed and reconstruction with a bone graft with soft tissue interposition arthroplasty may be performed.

[Slide.]

To the best of our knowledge or to the best of my knowledge, there have been no MDRs submitted to the FDA regarding the Braun-Cutter prosthesis by Sutter Corporation or Avanta Orthopaedics.

[Slide.]

In a summary of review of complications of bone

and socket joints in general, the primary prosthesis that was reported on was the de la Caffiniere, which is distributed in the United States and in Europe.

[Slide.]

The primary complication is loosening and the highest rate of loosening reported was 30 percent by Wyss in 1980.

[Slide.]

To summarize, the variety of surgical procedures available for the treatment of painful osteoarthritic thumb joint suggest that no single procedure is appropriate for every patient.

The ball and socket joint is just one treatment alternative for that joint. The product is safe, reliable, durable, and revisable. The ball and socket joint is used on the treatment of a relatively small number of patients.

The benefit to the subjects who are treated with this and similar devices outweigh the risk, and this is substantiated in the literature.

The removal of the device from the market is not warranted based on the published literature.

Thank you.

DR. BOYAN: Thank you. Before you sit down, let's just give the panel an opportunity to ask you any questions

directly.

Are there any members of the panel that would like to address any of the issues that were just raised? Dr. Greenwald.

DR. GREENWALD: I was just curious. I went down your list of complications, and retrospective as they were, to your knowledge, have there been any incidences of soft tissue inflammation?

MS. FOCHT: Not to my knowledge.

DR. GREENWALD: Or inflammatory response?

MS. FOCHT: Not to my knowledge, no.

DR. GREENWALD: I ask that only because titanium as a bearing surface in the lower extremity has more or less been abandoned.

MS. FOCHT: Right.

DR. GREENWALD: Because of the potential for titanium debris generation. Mind you, I am sure the loads are a lot less across the basal joint.

MS. FOCHT: I spoke with Dr. Braun in May and asked him that question, and he said that that was not a complication that he found.

DR. BOYAN: Yes.

DR. DAVID NELSON: I guess, first, if I could have a question for Ms. Nashman. Am I correct in saying that the

manufacturer is required to file an MDR if they are aware of a complication?

MS. NASHMAN: That would be correct?

DR. GREENWALD: Yes.

DR. DAVID NELSON: Okay. Therefore, it would appear that whoever was the manufacturer at the time would have been required to file MDRs, and hadn't been filed since you are aware of the complications in the literature.

MS. FOCHT: It is true that they can be filed from the literature, as well.

DR. DAVID NELSON: As well as if Dr. Braun is working with you, you know it from personal experience, so there is two different ways, and the MDRs probably should have been filed.

MS. FOCHT: If he reports them to us, yes, we certainly would file them.

DR. BOYAN: Any other questions? Yes, Dr. Skinner.

DR. SKINNER: I have one question. In the literature here somewhere, it says something about a cobalt chromium component.

MS. FOCHT: Right.

DR. SKINNER: You didn't mention cobalt chromium.

MS. FOCHT: Sure. We originally had a 510(k) that

was under review at the time that the PMA was made, and we had modified the articular surface to be cobalt chrome on polyethylene. We were then instructed to submit that as part of the PMA -- request to have that 510(k) application withdrawn and then submit that as part of the PMA application, and then at a later time we were requested to remove that submission and then submit it subsequently as a supplement.

So there was a point in time when the application did have a cobalt chrome polyethylene or proposed cobalt chrome polyethylene articular surface.

DR. RUDICEL: Can I ask a question?

DR. BOYAN: Yes. Dr. Rudicel.

DR. RUDICEL: I would like to know how many of these have been sold per year for the past few years.

MS. FOCHT: I can tell you how many were manufactured since 1980, which is approximately 430.

DR. RUDICEL: Since 1980?

MS. FOCHT: Right. We are talking really very, very small numbers for all of these devices.

DR. BOYAN: Dr. Rangaswamy.

DR. RANGASWAMY: My question is when you say that the benefits outweigh whatever risks are there, you are basing that comment upon the two articles by Dr. Braun

primarily?

MS. FOCHT: And conversations with Dr. Braun and others of our customers that use the de la Caffiniere prosthesis.

DR. RANGASWAMY: Right, but the written documentation is only those papers with his 29 and his 50 cases, am I correct?

MS. FOCHT: I believe there were other articles submitted, but Dr. Braun's literature is the primary literature that I reference, yes.

DR. RANGASWAMY: Thank you.

DR. BOYAN: Are there any other questions? Yes, Dr. Nelson.

DR. ROGER NELSON: Following up, the 29 and 50 cases, that was not clear whether or not the 50 cases published later included the 19?

MS. FOCHT: I believe so.

DR. BOYAN: Any additional comments? Questions?

[No response.]

DR. BOYAN: Seeing none, thank you.

I am going to turn the podium over to the FDA, and the first presentation will be by Ted Stevens, the lead reviewer.

FDA Presentation

MR. STEVENS: Good afternoon, Madam Chairman, ladies and gentlemen: I am Ted Stevens, a reviewer in the Orthopedic Devices Branch of the Office of Device Evaluation, and I will presenting the preclinical section of FDA's review of Avanta Orthopaedics' PMA for their Braun-Cutter Trapezio-Metacarpal Prosthesis.

I would like to thank Ms. Focht for a thorough presentation on behalf of the applicant, which should make ours somewhat shorter.

[Slide.]

FDA staff involved in the review of this application include myself, as the lead and preclinical reviewer, Dr. Stephen Nightingale, Medical Officer, Division of General and Restorative Devices, Gary Kamer, a statistician in our Office of Surveillance and Biometrics, and T.C. Lu, also of that office, who provided further statistical input.

[Slide.]

As you have heard, Avanta has proposed indications including inflammatory and degenerative conditions, trauma, recurrent dislocation and revision. These appear to cover most cases of painful or unstable trapeziometacarpal joints.

[Slide.]

The Braun-Cutter Trapezio-Metacarpal Prosthesis is

a total joint replacement for the basal thumb joint. The design is similar to a Chamley low-friction hip arthroplasty, in that it incorporates a metallic stem with an integral spherical head, and a polyethylene cup.

The stem is cemented into the proximal end of the metacarpal bone of the thumb. The polyethylene cup, which has a 3-millimeter peg, is cemented into the prepared trapezium.

Stems are available in three sizes, with the smaller head approximately 4.57 mm in diameter and a stem 17 mm in length, or with a larger 6.35 mm head that has either a 17.5 mm stem or a 25 mm stem. Two sizes of trapezial components correspond to the available head sizes.

The device is considered constrained, in that the ball snap-fits into the cup, preventing dislocation in more than one plane and providing a linkage across the joint.

[Slide.]

The device is made of titanium-aluminum-vanadium alloy and ultra-high molecular-weight polyethylene, both of which have a long history of use as biocompatible implant materials and which conform to voluntary standards as implant-grade materials.

The applicant provided a biomechanical analysis of each size of the device. Using an analytical approach, they

determined that the mechanical strength of the device components exceeds the stresses expected to be experienced by the device in vivo.

The device allows free rotation about the axis of the stem, and approximately 45 degrees of angulation in any plane away from the neutral axis, which falls within physiological requirements.

Sterilization of the device components will be by means of cobalt-60 gamma irradiation or ethylene oxide, both of which have been validated using appropriate standard methods.

[Slide.]

At this point, I would like to introduce Dr. Stephen Nightingale to present the clinical review of this device, after which I will address several questions to the panel regarding their views of the presented information.

Thank you.

DR. BOYAN: Thank you.

Dr. Nightingale.

DR. NIGHTINGALE: Thank you. I am Stephen Nightingale.

[Slide.]

The clinical information that the sponsor submitted to us in support of this application is listed on

this slide. We considered the first two of the paper that were submitted by Dr. Braun in 1982 and 1985. We did not formally consider the 1991 paper, although we were aware of it, because that 1991 paper states that additional patients were studied, but does not give individual case histories or any additional information.

In addition to that, the sponsor submitted actually 9 nine papers rather than 7 papers that are listed up there between 1980 and 1994, describing the de la Caffiniere. I have included 7 in my summary because 7 of the 9 papers have statistics that we were able to analyze.

The third thing that we did was both review the sponsor's and our own search for medical device reports, and neither the sponsor nor we were able to identify any of them.

Finally, our independent search, as well as the sponsor's, found 2 reviews, one published in 1989 and the other in 1995, which I will mention briefly, which discussed treatment alternatives for patients.

While we are on this slide, because I won't return to it again, our independent search for medical device reports was conducted basically by taking the search terms "thumb" and "prosthesis." When we did our Medline search, we exploded those two terms and felt that by the time we

finished our review was complete.

As I suspect all the panelists know, searching for medical device reports is something of an art, as well as a science. As I pointed out in my review, which the panelists have, we got to the point where we found 20 MDRs for one device and 12 MDRs for another device without finding a single MDR for this one, so we believe our search went through at least the most likely places, and we are comfortable with our conclusion that no medical device reports have been filed for this device.

[Slide.]

To repeat somewhat what Ms. Focht has already presented to you, the two basic papers were by Dr. Braun in 1982 and 1985, and we independently concluded on a textual analysis that the case report of 50 included the 29 patients.

There was 1 procedure per patient. We do not have in either of these papers individual case listings, so we don't know the mean age or the individual age of the patients or the sexes. It is not provided in the reports that were given to us, nor in the additional paper.

[Slide.]

What is provided in general is the underlying diseases of the patients. In the first paper, you can see

that 12 out of 20 patients had osteoarthritis, another 8 had rheumatoid arthritis. I have pluses for the remaining diagnoses. Dr. Braun doesn't tell us how many were in the categories, but we did not consider that essential to our review.

As you can see, in the 50 patient series that he published in 1985, the slight majority, 26 of them had osteoarthritis, another 12 had rheumatoid arthritis, and the remaining 12 patients had other diseases which are not specified in the text of Dr. Braun's paper, nevertheless, this gave us an overview of the patient population that he was treating.

[Slide.]

The outcomes of the patients -- to jump to the meat of our review here -- the followup in the first paper was 1 to 7 years. Dr. Braun does state that he did not include patients in his 1982 preliminary review who had been followed for less than 1 year.

The 1985 paper purports to be a complete review of his experience in his patients followed from 6 months to 10 years. Again, there is little pieces in the text where a blind woman is mentioned in both of those, and that was the basis of our assumption, I guess I should say, that the 50 patients includes the 29.

The basic outcome that you see there is loosening in 3 of the first 29 patients, and loosening in 5 of the first 50 patients. In other respects, the device seems to have performed satisfactorily.

There is a small typo here. Under "Painless Range of Motion," that is actually 22 out of 29. I apologize for that, and painless range of motion is not given for all 50 patients in the text of the second paper, but Dr. Braun does note that 26 of the 26 patients with osteoarthritis did achieve painless range of motion, just to quote to correct my typo there.

What Dr. Braun said in his text was that the remaining 7 patients who didn't achieve full painless range of motion, were not expected to achieve normal range of motion because of significant preoperative muscle imbalance of soft tissue, scarring, and contracture, such as proximal displacement of the carpometacarpal joint or fixed extension contracture of a metacarpal phalangeal joint.

[Slide.]

The sponsor submitted a comparison of the Braun-Cutter to the de la Caffiniere prosthesis. We did not attempt a formal analysis of either success or implant survival other than to note that they were roughly comparable.

The reason for presenting this slide was that we found that the mode of failure for both devices was basically the same, they loosen up. Whether this is due to operative intervention or trauma, loosening occurs with finite and roughly comparable frequency within the two devices.

[Slide.]

Finally, to summarize our review of the ancillary literature, this is a table taken from the second of two parts of a review in the 1995 American Journal or Orthopedics by Dr. Pomerance of Temple University, where he reviews the five major modes of treatment.

Excisional arthroplasty, he cites the advantages, which probably the audience will have trouble seeing, but I think that the panel is already familiar with these. There are both advantages and disadvantages to them.

Fusion, similarly, has advantages. Roughly moving in chronologic time, down the rows, it is really in the seventies when total joint arthroplasty was introduced, for example, by Dr. Braun, and what is noted there is that the advantages are on the left. The disadvantages, what he notes is that it is technically demanding and that there is implant loosening, and according to the reviewer, did not achieve widespread acceptance and must have adequate bone

stock.

Dr. Pomerance goes on to note that silicone implant arthroplasty achieved certain prominence in the eighties, and more recently it would appear that ligament reconstruction is at least in some surgeon's opinion, the treatment of choice for many patients. However, Dr. Pomerance's conclusion was that no single mode of therapy was clearly advantageous for all patients, and I guess that was ours, as well.

DR. BOYAN: Thank you.

DR. STEVENS: Thank you, Dr. Nightingale, for your presentation.

I would now like to read four specific questions that FDA has for the panel regarding the information presented in support of the Avanta Orthopaedics Trapezio-Metacarpal Prosthesis.

First, are the proposed indications supported by valid scientific evidence and are there any specific contraindications, warnings, or precautions you believe are appropriate for the use of the device?

Second, are there specific clinical evaluations or tests that you believe are necessary for the selection of appropriate patients?

Third, should any additional or special

instructions be added to the surgical technique for the Avanta Braun-Cutter Trapezio-Metacarpal Prosthesis?

Fourth, should any specific information be given to patients regarding the device or their surgery, such as limitations in activity or rehabilitation?

Thank you for your attention. This concludes FDA's presentation.

Dr. Boyan, I would now like to turn the reins back over to you. Do you have any questions?

DR. BOYAN: Thank you. Let me open it up to the panel for questions. Just so that everybody knows, we are going a little bit more quickly than we had thought, and so we are going to -- unless there is an outcry against this -- we are going to not have the break. I think we are progressing very nicely. If there needs to be a break, just indicate to Jodi or me, and we can see where we are and arrange one.

Let's have you sit down I think now unless there are specific questions to be addressed to you. Do we have any specific questions?

[No response.]

DR. BOYAN: Let's go ahead and have the presentation by Dr. Rangaswamy and Dr. Besser, and then we can have a general discussion and address the questions to

the individuals as appropriate.

Dr. Rangaswamy, could you give us your clinical review?

Panel Review

DR. RANGASWAMY: Actually, the FDA has probably reviewed it, and everybody else has, too. I have more questions myself really more than summary of the review which has been done, and the problem is basically, you really have one paper of the 50 patients that we are looking at, but the minute that you don't get the ages of the patient at all to look at, then, the question to me is how can you then make recommendations based upon their indications for use, because you would have to tie it in with the particular age of patient that you would use it for unless the diagnosis was different, I don't know. So that was my concern.

The other thing is obviously they haven't specified the gender, but that is not such a critical issue, and you don't even know what disease 25 percent of the patients had. So that again makes it very difficult to sort of go back and use.

Dr. Boyan, is that all right for me to do it in this sense, so I can just finish it?

DR. BOYAN: Yes, fine.

DR. RANGASWAMY: The other major concern I had was again I am not sure of how much time they had to prepare or to get all the data together, but if you give someone six months to look it up, and the question was would it not have been more feasible for them, for the sponsor, to have even designed something like a very quick SF-36 kind of questionnaire or something sent to the patients, track them down to see how many were alive still at this point in time, which would have (a) given you the ages of the patient and how many were around, because then you could have come up with where they were today, because that paper, I think the second paper was 1985, so we are talking about 14 years ago.

The next point is that six months is nothing in terms of followup. We don't even know how many patients had more than two-year followup, so if you can then identify how many of those patients actually had a two-year followup, and then pull out those patients and then look at them, and then present it, even though it is not part of their paper, it could have been done.

Just to present -- that was my biggest difficulty with this -- just to take that paper and then say, well, you know, we don't have a clinical study or we don't have preclinical studies now, but we will just use this as the data, doesn't seem like a lot of homework that had been done

on this I think.

Maybe they weren't given the guidelines or something for it, but that really should have been done I think, because right there you have another problem. Suppose two-thirds of those patients had less than two-year followup, or let's say even half of them had less than two-year followup, then, you have got a very small number, and then you keep sort of dwindling it down and you are left with handful of patients.

So even though it may not have had great risks or produced any kind of major catastrophe, I think you have a problem there.

I think the last thing that I had to talk about was they provided a lot of the standard literature. All this is old literature really in a sense that has been available because nothing really new has been written except I think a couple of chapters in some instructional course, and the Academy's journal had a new article on it, and they bring up some very interesting issues, all of them.

The question is the indications for the patients, the goals and how do you specify this to the patient as to what you hope to achieve from this, and that really isn't even touched upon.

The last one is the limitations of any of these

procedures, particularly this one, and in a rheumatoid patient, in particular, what would be the dangers of that.

So my thing was that that was the kind of clinical data that I would have wanted to see to be able to decide, you know, is this something. It is probably safe, you know, that is not the issue, is it effective is the question, you know, it may be partially effective.

The last thing is it is a technically demanding procedure. They have only manufactured 430 in the last 17 years, 16 years, and we only have data really on 50 and documented data, so let's say even if you had data on all of them, it's a small number, a technically demanding procedure, you always have to worry about how it is going t be used and who is going to use it, and particularly in a patient, say, with rheumatoid arthritis or an older patient who is a little cachectic and just doesn't have enough soft tissue.

So those are some of the clinical issues I think have just not been addressed.

That's it, Dr. Boyan.

DR. BOYAN: Thank you very much, Dr. Rangaswamy.

Dr. Besser, can you give us the preclinical review?

DR. BESSER: Yes. I had a couple of concerns in

that although the manufacturer provided a theoretical analysis for the loading of the prosthesis, no data was presented for actual testing of samples of the prosthesis.

MS. FOCHT: I don't know if that was originally performed when the device was cleared to the market.

DR. BESSER: I am not sure either.

DR. BOYAN: Dr. Besser, let me repeat the answer as I think I heard it. The answer was that you were not sure that the analysis that he is asking about was performed when the device was first introduced into the market, is that correct?

MS. FOCHT: Right.

DR. BESSER: Whereas someone mentioned that this was similar to a hip prosthesis, it is a ball and socket joint, it is not a hip prosthesis, I mean the loading on the thumb is orders of magnitude away from the loading on the hip, and I don't expect a whole lot of these to fracture, you know, or the failure modes that you would see in the hip prosthesis to occur in a thumb prosthesis in normal use.

But you listed as a contraindication patients with "extremely high levels of activity." To me, I am not sure how high those levels of activity have to be, and I would like some I guess clarification either in the information given to the physicians for contraindications for use and/or

the information given to patients as to just what levels of activity would be appropriate or possible using this prosthesis.

I also have a question. This is my first panel meeting, so I guess this is sort of procedural. The fact that no MDR reports exist, does it mean that they shouldn't exist? The question asked earlier where some of the things listed as failures in the articles by Braun would have been the type of events that should have been reported as MDRs?

DR. BOYAN: Could we have a clarification on that? Yes, Dr. Nightingale.

DR. NIGHTINGALE: There are several different ways that adverse events can be recorded both in FDA and, say, ECRI databases.

DR. BESSER: I am sorry. What is ECRI?

DR. NIGHTINGALE: You asked me that question at the wrong moment. Mr. Stevens, what does ECRI stand for? I apologize. We searched it.

DR. BOYAN: But the statement is, it is a database?

DR. NIGHTINGALE: It is a commercial database.

DR. BOYAN: We can clarify that later. Go ahead with the answer.

DR. NIGHTINGALE: What we tried to do was to

search every known database, everything we could find on Internet in electronic filing, and I think we had six databases, and I am scared to tell you the other four because I might not remember those acronyms either, but we do have professional librarians at the Center, and what I did was went to our professional librarian and did the search with him. I have a copy of that search if you would like to review it.

DR. WITTEN: Maybe I can just clarify about the MDR database.

DR. BOYAN: Yes, Dr. Witten.

DR. WITTEN: That is the FDA MDRs, and those can be reported by anyone. It could be by an institution or a practitioner.

DR. NIGHTINGALE: It is mandated.

DR. WITTEN: It is mandated, but I don't think it was at the time. There has always been an availability of the reporting, but that is right, it has only been mandated fairly recently.

But if these were events that were in the article, that doesn't mean that they were reported to the sponsor and that the sponsor then -- they were events that if they were reported now to the sponsor, the sponsor would be expected to report them to the FDA, but these could be things just in

literature, which we would expect now that the practitioner would report directly, but that wasn't the case at the time that these articles were written.

DR. BOYAN: Mr. Melkerson, did you want to add something to that?

MR. MELKERSON: Just a followup to Dr. Witten. In 1990, the Safe Medical Devices Act incorporated user facility reporting, and a surgeon or a user facility would be required to make a report of those types of adverse events. Under MDR, it is only if those reports are submitted to the manufacturer and with complete information are they required under the regulation to report under MDR. If they had incomplete information, there would not be a report necessary.

DR. BOYAN: So to summarize where we are now, as I understand it, the MDR would be required now. At the time that Dr. Braun wrote his article, that was not necessarily the case, and these reports are in the literature and are available to us now.

DR. NIGHTINGALE: Yes.

DR. BOYAN: Dr. Besser, do you want to continue your review?

DR. BESSER: I guess my only other comment was that there doesn't seem to be a whole lot of biomechanical

analysis in this situation. The only other thing that I did notice, in one of the papers by Dr. Braun, it did mention that when I guess the carpal component was implanted too deeply and therefore you had impingement of the joint, which caused loosening, I guess this goes back to Dr. Rangaswamy's comment about the technical expertise required by the surgeon.

I guess in the instructions given to the surgeon, I am not sure how detailed those instructions are and I would I guess defer to Dr. Rangaswamy, but this situation where the implant was I guess misimplanted changes the biomechanical loading on the implant and caused a loosening problems.

For this analysis, this was all for the cemented prosthesis?

DR. BOYAN: Ms. Focht, would you like to respond to that?

MS. FOCHT: We did not make an analysis on the bone-cement interface, if that is your question, and Dr. Braun used the device, cemented and uncemented, on the metacarpal side, and it is my understanding that the trapezial side is always cemented.

DR. BESSER: And in the results, there was no differentiation between those two sets?

MS. FOCHT: He reported some subsidence on the uncemented cases, on the metacarpal side.

DR. BOYAN: I think what we need to do here is, Dr. Besser, if your review is complete, then, what we should do is open this up to questions from the panel.

DR. BESSER: Yes.

Panel Discussion

DR. BOYAN: Why don't we go around in an orderly fashion. We can start over with Dr. Skinner and everybody have one opportunity to take a pass at either the company or the FDA or else you are also free to make a general comment, and then after we have each had a chance to do it one time, then, we can open it up for people that have greater detail that they would like to address.

Dr. Skinner, do you have any specific question?

DR. SKINNER: Thank you, Dr. Boyan. I have a couple comments I would like to make.

First of all, I agree with Dr. Besser. It is somewhat concerning about the lack of testing of the prosthesis. The only reassuring thing about that is that in the reports that have been provided, there is no evidence that there is significant breakage or damage, and it is quite concerning about the loosening, and that makes me worry about perhaps the prosthesis not being optimized in

its design.

Based on that, I would like to ask Ms. Focht if the minimum thickness of the polyethylene in the sort of cup component, what that is. Do you have any idea? I couldn't tell from the mechanical engineering drawings.

MS. FOCHT: I don't know that number off the top of my head, no.

DR. SKINNER: Then, Dr. Rangaswamy made some comments about the poor literature, and I agree with that, but I think that we can make some deductions regarding the literature.

First of all, we know that those patients had to be adults, so we know they are over age 18, something in that range, and I don't think any surgeon would put them in a child, and I think that is a contraindication.

As to the concerns about the disease state, I don't think that is a concern either, because when the CMC joint is destroyed, it is basically the final common pathway. Whether it is destroyed through rheumatoid arthritis, trauma, degenerative arthrosis, whatever, it is still a destroyed CMC joint. So I am not too concerned about those sorts of indications.

That is about the sum of my comments.

DR. BOYAN: Thank you. Dr. Greenwald.

DR. GREENWALD: I have some comments and I have some questions. It is easy to sit here in 1997 and be a Monday morning quarterback on what should have been done preclinically or during the clinical evaluation of a device, but we are looking back now many years, and I think in the end, the final proof of the pudding, preclinical evaluations being deficient or not, that there is at least some clinical information in the literature which describes efficacy.

I would point to Dr. Braun's paper where if you looked at his commentary, over a 10-year period there was a 90 percent survival of the device. That being a limited paper, but still it is a perspective, and given the fact that approximately 480 of these were manufactured, and I assume they are all implanted, not all by the same surgeon, it does give some evidence, however narrow, efficacy of the device.

I do have a question that I wanted to ask the Food and Drug Administration. To your knowledge, how many other companies are likely to -- I don't want to use the word benefit -- but are likely to gain from a recommended approval of this PMA, that produce ball and socket articulations for the phalanges or carpal joint?

MR. STEVENS: Dr. Witten, do you want to answer that or do you want me to?

DR. WITTEN: This is a PMA, so if you are asking whether another company that made a similar device --

DR. GREENWALD: No, no, no, that is not what I am asking.

DR. WITTEN: I am not sure what you are asking.

DR. GREENWALD: I guess that is what I am asking. We are evaluating a specific PMA on a specific device.

DR. SKINNER: It is basically a patent because it is a PMA for one device.

DR. GREENWALD: Right. Dr. Nightingale?

DR. NIGHTINGALE: I can answer you in the context of the information in the sponsor's application, and the sponsor did submit evidence about a single competing device. The sponsor only submitted evidence for a single competing device. I am trying to walk a narrow regulatory pathway there, and Dr. Witten may have more latitude than I do.

DR. GREENWALD: I appreciate that.

DR. WITTEN: I think if your question is what evidence would we expect from the next PMA of a similar type of device?

DR. GREENWALD: I was wondering, these are not the only ball and socket articulations that I am aware of that have been used in the joints of the hand. Yet, this is the one company that has come forward with a PMA for their

specific device. I just wonder whether or not there is other information in the literature. You cited one other company by reference, but I think of a number of other companies that produce similar devices.

In one sense, I guess it is just a general comment rather than a critique of this particular PMA. What I am struck by -- and I want to repeat this -- is I think the panel has to weigh very carefully the weight of what has been presented in lieu of the clinical utilization of this device for the particular indications that are being submitted, and albeit the literature is narrow, and I have said this, there is an indication that there is a reasonable degree of efficacy associated with at least the Braun report.

DR. BOYAN: Thank you, Dr. Greenwald.

Dr. Rudicel.

DR. RUDICEL: I would just say in conjunction with that, since we are moving retrospectively, I am wondering if the indications for the device, now that it is 1997, need to be any narrower given that there has been a progression of ways of treating this disease.

DR. BOYAN: I think that is something that as we go down through the specific questions that FDA has asked us to address, that will be addressed there.

DR. RUDICEL: One other question. I am curious if more than one surgeon has purchased these devices.

MS. FOCHT: Yes.

DR. BOYAN: The answer to that was yes.

Dr. Rangaswamy?

DR. RANGASWAMY: I would like to ask the questions about the age. I did not assume that they would put them in children, but I guess the question was really the age category. When you have listed six lines of indications for doing this particular procedure, I guess in the rheumatoid patient even today, excision arthroplasty, together with reconstruction of the ligaments, seems to give an equally good result, and the question that always bothers me I guess -- and I am sure this is just probably a philosophical thing -- is that is this a new, improved, you know, it is like you get a new, improved detergent on the market, it doesn't make too much difference, it is not new, but it is a different way of doing things, does it need to be much more clarified and similar to what Dr. Rudicel just said, I think you do have to hone down on the indications.

People say, well, I didn't like the old procedure, it didn't do so well. So it goes back to I think what Andy Wyland said in his review, is that you have to identify exactly what your goals are for a particular patient.

If it just pain relief, and this is very limited activity, and you look at it, we have started looking at these things much more now, you know, patient outcomes are being looked at differently, so there is a whole different way of looking at things, I think, than we did many years ago.

So that is really what my issue was, and the question was about the status of the rest of the hand. It does make a difference what your underlying disease process is, if the rest of the hand doesn't look good and the soft tissues aren't good enough. So that was still my concern about that.

It still goes back, I know we say that there is 90 percent survival and there is so many percent. They still don't give you all the "n" values. They don't tell you exactly what numbers we are talking about and how they came up with those figures. One can live in the land of percentages and be very happy that it is great, you have 10 patients, 9 did very well, so you have got a 90 percent survival rate, that's wonderful. It is not really wonderful, it is not -- you can't take that data and transpose it someplace else, and I guess that is my concern, that you take data from here, because this, I think is a kind of model as to what would happen in the future for any

other kind of device.

You set up a precedent that you are prepared to accept that is inadequate and is just not answering all the questions that you would like answered. You can still try to retrieve something from it. It seems safe. That is not the issue.

The question is, is it effective. Maybe in a very small group of patients, so you are honing down your indications again.

DR. BOYAN: Dr. Besser.

DR. BESSER: I have a question for Ms. Focht. Of the 480 that have been manufactured, are most of them implanted?

MS. FOCHT: To the best of my knowledge. I don't know the exact number that was implanted, no.

DR. BESSER: I am just wondering whether we are seeing a report of 50 cases out of 200 or out of 400 that have been implanted. I guess the time period in which they were implanted, were most of them implanted 15 years ago or have they been sort of spread out over the past 15 years, do you know how you have been selling them?

MS. FOCHT: I would say the bulk of them were sold in the 1980s, and Dr. Braun's most recent article in 1991 reported on 100 implants used with 10-year followup, a

maximum of 10-year followup.

DR. BESSER: Okay. They weren't all 10-year followup, they have been over the past 10 years. Okay.

DR. BOYAN: Coming around to Dr. David Nelson.

DR. DAVID NELSON: I think it is important that we recognize -- and I guess I am speaking now mostly to my fellow panel members -- that we really have got the cart before the horse in this particular case and actually in the other two parts we are looking at tomorrow.

That is, we did the human experiment prior to doing the PMA, which is usually not the way we do things or at least not the way we are supposed to do things, but that is not really the company's fault because they were given the 510(k) before we asked for the PMA.

So we are faulting your studies and we are criticizing you, but it is not your fault, it is really our fault because we didn't ask for that data before it was released to use in people.

I think it is also important to remember that although Braun does not equal Avanta, the Avanta-Braun prosthesis, they are highly interrelated, that is, there is a flow of information from Braun to Avanta and presumably money from Avanta to Braun, so we are asking for information from the company when it has come from Braun, and, you know,

it is kind of funny. He may have done a bad study, but it is not their fault.

DR. BOYAN: Ms. Focht, would you like to address that?

MS. FOCHT: Yes. I would like to say you shouldn't presume that there is a flow of money from the manufacturing organization to Dr. Braun.

DR. DAVID NELSON: All right. I apologize. That was a presumption. My point was just that the two are related, but people I think, I feel are criticizing you when it is not your fault. It was the study that was published, that has maybe not given you all the data you wanted.

Seth, you were starting to say something.

DR. RANGASWAMY: We are not criticizing them.

DR. GREENWALD: I think you are very much on the money. You know, you are right, the cart is before the horse. I mean this company was issued, along with any other companies that had these particular type of devices, 510(k) permission to sell these devices, and now, through an attempt to put the house in order, so to speak, we are being asked to look at what, in fact, has been presented and to make a determination is there sufficient information that describes safety and effectiveness, however minimal the preclinical studies may have been, and however minimal the

available clinical information is, as to whether or not these devices should, in fact, receive PMA application and remain in the marketplace, because denial will, in fact, facilitate their removal.

That may prove a burden both to patients and implanting physicians, however small this number may be.

DR. DAVID NELSON: Right. I understand that from this morning's discussions. Thank you.

DR. BOYAN: Thank you. Dr. Roger Nelson.

DR. ROGER NELSON: Again, we are looking at this retrospectively, so I have some questions related to the article itself in terms of looking at the issue of efficacy.

All of the studies, the followups were done by one surgeon, then, we can assume that 50 patients were done by Dr. Braun or not?

MS. FOCHT: I think so in his practice.

DR. ROGER NELSON: Right. So that we are only looking at the efficacy of Dr. Braun doing the surgery, we are not looking at the other surgeons that have been using the other 400 or so.

MS. FOCHT: Yes, there was no published literature from other surgeons using that device.

DR. ROGER NELSON: So that is one of the major issues. The other issue is that when we look at this

efficacy issue, we are saying, well, there are no failures or 90 percent success rate, only 10 percent failures, and the failure being a total rejection, if you will, of the device. That is correct?

DR. NIGHTINGALE: Yes.

DR. ROGER NELSON: But, in fact, we haven't looked at the total patient. I might have a failure and might choose -- if I had it in my right hand -- I might choose to become left-handed, but it wouldn't be reported as a failure because it will be so painful or maybe perhaps not useful in terms of function.

What I was trying to get at is -- again you can't answer this in issue posed -- but to look at the hand function, we have no mechanism of looking at people after this device was implanted to look at their function and indeed whether it made their quality of life any better or different. Right? We are just assuming that if we have an incidence of failure, that the failure meant that the thing broke or did something, and that was a failure.

But we don't have any idea of whether or not this device is in there, but it is kind of, oh, I feel it is a painful thing and I will just live with it because I don't want to go back to that surgeon.

I would assume that is correct, right?

DR. NIGHTINGALE: Yes.

DR. ROGER NELSON: The other thing that concerned me was the report in the literature that 22 patients achieved full range of painless motion, and then 26 achieved good range of motion, which wasn't clarified in terms of what motion it was, in terms of degrees.

So I may have 5 degrees of motion, but it is good, painless motion. Is that right? I mean that is the way I would read this. I don't mean to be a --

DR. NIGHTINGALE: No, no. I mean we are reading the same paper. The way I read that paper was the 22 patients had full and painless range of motion, and that the remaining 7 patients had variable degrees of motion.

I think my reading of that paper, which is simply my own, is that the 3 patients who fractured, whose devices loosened, 1 because of the operation, 2 because of trauma, may or may not have had full painless range of motion, but Dr. Braun did not claim success for those 7 patients. That is how I read it.

MS. NASHMAN: A quick formality here. If you all could state your name for the record before you make a comment, it would be appreciate for the transcriptionist.

DR. NIGHTINGALE: I apologize. The last person to speak was Stephen Nightingale of FDA.

DR. ROGER NELSON: Okay. That covers it.

DR. BOYAN: Dr. Silkaitis.

DR. SILKAITIS: In terms of the call for PMA here and the company being prepared for it, I believe there is a logistical factor that should be taken into account, in other words, I believe they were required to submit this within a 90-day time period.

There was a request for additional clinical, possibly going out and getting additional clinical data. That becomes logistically difficult to do if the company is being asked to do something like that, especially since the product that is under evaluation has a 15-year market history, and only 450 over that time period. There isn't very many prostheses out there.

The other thing I guess would be logistical, is that since I am assuming that the clinical work that was done at the time was done on a marketed device, so therefore an IDE was not put together, so therefore patients were not consented and would volunteer for a study. So then trying to go back and get these patients to volunteer may not be feasible.

That is it.

DR. BOYAN: Thank you very much. Dr. Holeman.

DR. HOLEMAN: Thank you. My comments will kind of

relate to what Dr. Roger has said and also Dr. Rangaswamy. It has to do with the indication for use, especially when it comes to the indication that you said for pain. I am not sure that any of the data that were presented demonstrated that it actually provided relief of pain. As a matter of fact, the sponsor stated that one of the advantages that pain relief may be achieved, but that also says that it may not be achieved.

The other thing in relation to that has to do with the fact that it was stated that the implantation of this device may not meet the patient expectation or that the patient expectation may deteriorate over time.

That statement suggests that perhaps the patient and the doctors were entering into this procedure with different expectation of what the outcomes were to be. It kind of bothers me that no attempt or no indication in the literature indicated that at anytime that anyone assessed the patient comments on satisfaction with the device, the performance, to what extent was the patient able to perform activities of daily living after the implantation as opposed to before the implantation of the device.

I think that when we look at outcomes based solely on the life of the device itself as opposed to the outcome and benefits to the patient, I think we leave a lot of data

as far as effectiveness unanswered or questions unanswered.

DR. BOYAN: Thank you. Everybody has had an opportunity to ask at least one or a series of questions. Now, there may be some people that would like to go into greater depth or have additional questions that have come to mind. Anybody on the panel? Dr. Rangaswamy.

DR. RANGASWAMY: At the risk of upsetting everybody, this is not directed against the company or anything of the sort. The comments are purely made on the basis of the paper that is being used.

I guess my question is it was written in 1985 in Clinical Orthopedics. As Swanson wrote about his silicone arthroplasty -- I am not using that -- but just as in early 1970s, and even at that time, the Society for Surgery of the Hand did have a method of evaluating patients. You had a method of at least finding out if something was good in terms of function, pain, whatever they are doing, activities of daily living, and here is someone who is trying out a new implant at that time, and has not done that.

If you look at the result section of what has been published in the Clinical Orthopedics, it is like a chatty little section. It doesn't tell you anything at all, and I guess that is what I am keeping on going back to, is that there an opportunity at that time, it wasn't done, but

neither was it done subsequently, you know, in terms of looking at and establishing clear-cut objective criteria that you could look at.

I am not saying a patient needs great function, you are absolutely right. They could probably work with 5 degrees of function, because that would be adequate for that patient, and that patient maybe just wants to be able to do something very simple.

So that is again going back to looking at effectiveness. There is the whole issue of safety and then effectiveness, and I think that was really what I was trying to point out to you. It wasn't against any company or even against Dr. Braun or something, but you are using this data, and if you are going to start this, either you decide you are going to have science or you are not going to have science, and you are going to rubber-stamp everything.

That is my concern about this. If it is a question that we are going to rubber-stamp things, well, then it is very easy to do it. You can accept whatever data there is and look and see that there aren't any sort of horrendous complications and just take it that step further, or you can go in and look and see is there a way to salvage this and is there a way to kind of take something out of it, and I think there is. I don't think it is impossible, I

think one can certainly do it.

DR. BOYAN: Dr. Nelson and then Dr. Skinner.

DR. DAVID NELSON: Ms. Focht, just a brief question. You said that there was no other published information. Do you have any unpublished information that would help us on this? Has the company, for instance, done an internal study or anything?

MS. FOCHT: No.

DR. DAVID NELSON: Thank you.

DR. BOYAN: The answer to that question was no, there hasn't been any other studies done.

Dr. Skinner.

DR. SKINNER: I haven't reviewed the information that the people from the FDA have reviewed. I have looked over the abstracts -- and I would hope they would correct me if I am wrong -- but it is my understanding that the de la Caffiniere prosthesis is an extremely similar prosthesis, and there are multiple publications on it indicating roughly the same results as Dr. Braun obtained.

Is that not correct?

DR. NIGHTINGALE: That is our impression also.

DR. SKINNER: So basically, what I am saying is that we are not basing this on one report, we are basing it on a very similar prosthesis. The results seem to be

translated even across the ocean. It is not a different prosthesis, it is very similar, and I think that that data should be taken into consideration in evaluating a class of prostheses, and I think that is what we are talking about here.

DR. BOYAN: Mr. Dillard.

MR. DILLARD: Thank you, Dr. Boyan. There is a couple of things I think I ought to clarify at this point, that have been talked about, and I think it is a good time, one of which is that this premarket approval application needs to stand on its own based on the data in the product. This is not a situation where other data from another prosthesis can be used in support of the approval of the application for another product, so from that standpoint, while it may be interesting published information, it should not be used in support of your recommendation today here on this product.

The other is a question that, Dr. Greenwald, you brought up earlier, and if you wouldn't mind maybe restating it, if you can remember it.

DR. GREENWALD: I don't think senility has overtaken me yet, but just refresh my memory a little bit.

MR. DILLARD: I think you had raised a question about the 515(b) type PMA applications and the preamendments

nature of the product.

DR. GREENWALD: Right. We talked about the devices that we are now talking about today and tomorrow are preamendment devices for which 510(k) approvals were given. A number of years have gone by. These products have been in the marketplace and on the market, however limited in number and application, and now, because of the Safe Medical Devices Act and the call for PMAs on these preamendment devices, we are now evaluating the PMA that has come in specific to the application here.

I think, as Dr. Nelson correctly put it, it does seem in some way putting the cart before the horse, but nevertheless, that is the reality of where we are in 1997.

Am I on target here with what you said?

MR. DILLARD: Thank you. I just wanted to make sure I had it clear what one of your issues was.

DR. GREENWALD: Let me just finish this then. What I went on to point is that although these have enjoyed -- these products, these disused or minimally used products have enjoyed 510(k) utilization, currently, if these PMAs are found unapprovable, they will subsequently be removed from the marketplace, at least that is my understanding of it.

MR. DILLARD: Yes. Good. And I would like to

clarify that a little bit also, and you made one other point about the status of any of the other products that you may be aware of, and any of you on the panel might be aware of, and their current status based on the fact that they are not here today, where does that leave them, and so I would like to clarify that a little bit.

I think I will take that latter point, which is any of the other products that might have either been on the market preamendments or had been cleared through the 510(k) process, as of the December time point, which would have been 30 days after that final Federal Register Notice in September, the products that were not submitted under PMA application or did not have an investigational device exemption submitted to the FDA, should be off the market. They should not be marketed any longer because it takes either an approved IDE application or a PMA application under review for the products to remain on the market.

So based on today's standards right now, this product is the only one that is a legally marketed product in the United States. Everything else should not be marketed. So I hope that clarifies the one other point that you had.

The other is that the level that we look at for substantial equivalence versus safety and effectiveness is

different. Substantial equivalence at the time that these were found to be preamendments Class III devices, the level to obtain marketing was substantial equivalence to that preamendments device.

As of December of 1996, 90 days after that final call, a product needed to have a PMA undergoing and that there needs to be reasonable assurance of safety and effectiveness of the product, and the product needs to be then either approved or not approved under a PMA to have a final status on that product.

Just to drive home, not to be repetitive, but that product needs to stand on its own based on the information on that product, not on the fact of a whole class of products, because it no longer is that situation that we had when it was substantial equivalence.

I hope that has helped.

DR. BOYAN: Thank you very much.

I just want to give one last opportunity for general questions to the panel before we go to addressing each of the questions from the FDA to us.

All right. Seeing no issues being raised, as we turn it back over to the FDA questions, I would like to compliment Mr. Stevens and Dr. Nightingale on your review of this application. It was very nicely done.

All right. Panel questions. Could we have the overhead back up. Does everybody have their panel questions in front of them?

I am just going to repeat the general questions, so that we are clear on what we are going to address, and then we will take each question in turn. As we go through each question, we will just go right around the table, only this time we will start with Dr. Holeman, and then people that have a comment relative to the question will offer them, and then we will start with the second question, the reverse, so you understand how we are going to do it.

Our first question that we are going to look at is: Are the proposed indications supported by valid scientific evidence? Continuing the first question: Are there any specific contraindications, warnings, or precautions that you believe -- that is we -- believe are appropriate for the use of the device?

The second question: Are there specific clinical evaluations or tests that we, the panel, believe are necessary for the selection of appropriate patients?

The third question: Should any additional or special instructions be added to the surgical technique for the Avanta Braun-Cutter Trapezio-Metacarpal Prosthesis?

Finally, the fourth question: Should any specific

information be given to patients regarding the device or their surgery, such as limitations in activity or rehabilitation?

Again, the first question, which is the one we will address first: Are the proposed indications supported by valid scientific evidence? And are there any specific contraindications, warnings, or precautions that we believe are appropriate for the use of the device?

Dr. Holeman, why don't you begin.

DR. HOLEMAN: The only thing that I would say in reference to the indication being supported, I think we are knowledgeable and we are aware, we all agree that the amount of data that we have at this point are limited as to support of the indication for use, and I would say that based on the fact that I am still not sure if pain is one of the indications for use, that it has even been discussed adequately as to whether or not it achieved that.

DR. BOYAN: Thank you. Dr. Silkaitis.

DR. SILKAITIS: My comments will be brief. Basically, evidence has been provided by the manufacturer for a limited indication for their product.

DR. BOYAN: Dr. Roger Nelson.

DR. ROGER NELSON: And I would agree that there is limited evidence, scientific evidence perhaps, but very

limited evidence by one surgeon, by his technique, without having a broader spectrum of surgeons involved in the care of the patients and followup, and again, we are looking at it after the fact.

But I would say that there is very limited scientific evidence and that there would have to be very significant indications for this surgery.

DR. BOYAN: Dr. David Nelson, and would you also address some of the contraindications or warnings.

DR. DAVID NELSON: I have no concerns on these issues.

DR. BOYAN: Okay. Turning it over to Dr. Besser.

DR. BESSER: I am addressing the first question, are the proposed indications supported by valid scientific evidence. The evidence that is presented is valid, I don't think it's convincing. I have no comment on specific contraindications, warnings, or precautions.

DR. BOYAN: Dr. Rangaswamy.

DR. RANGASWAMY: I guess everyone has heard my comments on this. I think there are indications for the procedure for putting in this kind of implant. They are limited, and if it is marketed, it has to be based on the fact that this is one surgeon's experience at this point in time.

Times are different. One can make excuses for the past, but I today, it is very difficult to use a broad variety of indications, and my concerns would really be with the patient who has severe rheumatoid arthritis, whether this is really a device to be used in that kind of patient. It seems to be more in the isolated osteoarthritic CMC joint of the thumb sort of patient who has this, where this can be an option of treatment.

So I think it is very limited. I am not sure that the data is all that good, and that is still my concern about it. There is not enough data.

DR. BOYAN: Dr. Rudicel.

DR. RUDICEL: I would agree with that, that the indications would need to be narrowed and that there is not a lot of data to support them.

DR. BOYAN: Dr. Greenwald.

DR. GREENWALD: I feel that the presentation is limited by the addressing of one study and this one surgeon's one experience, but by the same token, so is the indication for the number of these devices that are indeed to be implanted or are likely to be implanted.

It would seem to me that that being the issue, I am really not particularly bothered by the minimization of what we have, in fact, read here.

DR. BOYAN: Thank you. Dr. Skinner.

DR. SKINNER: Could I ask Dr. Nelson to please clarify what he meant by whatever he said. What was that?

DR. DAVID NELSON: I said I have no concerns about the data. We don't have any scientific data, and we don't have anything appropriate for the indications, but that is not the fault of the company. It is the nature that we are doing this backwards, and I am willing to accept the limited data and the fact that there are no significant adverse effects of it.

DR. SKINNER: So you are basically willing to accept the list of surgical indications noted in the handout here.

DR. DAVID NELSON: Yes.

DR. SKINNER: I agree with Dr. Greenwald and I also agree with Dr. Holeman. I think that the list has a small problem with it in that I think that all of them except the last one are appropriate indications because I think that is basically a common endpoint, but I think that they all should have "painful" placed before them, because the indication should be painful degenerative or inflammatory disease, painful degenerative basal joint arthritis, painful dislocations, subluxation. I think that should be the indication. I think they should all be.

DR. GREENWALD: I would agree with that.

DR. BOYAN: Thank you very much.

Let's go the second question. If you don't have a specific comment to make, don't feel obligated, you can pass it to your neighbor. We will start this time with Dave Nelson and go this way around the room.

Question No. 2: Are there specific clinical evaluations or tests that you believe are necessary for the selection of appropriate patients?

DR. DAVID NELSON: No.

DR. BOYAN: Dr. Roger Nelson.

DR. ROGER NELSON: No.

DR. BOYAN: Dr. Silkaitis.

DR. SILKAITIS: I have no comment.

DR. BOYAN: Dr. Holeman.

DR. HOLEMAN: No.

DR. BOYAN: Dr. Skinner.

DR. SKINNER: I am sorry, Dr. Boyan. What was the question?

DR. BOYAN: This is our second question. Are there specific clinical evaluations or tests that you believe are necessary for the selection of appropriate patients? You can think about it for a while.

DR. SKINNER: Well, I think that there should be

x-ray evidence of one of those conditions as typically found in the Medicare regulations for total hip replacement, for instance, but other than that, no.

DR. BOYAN: Dr. Greenwald.

DR. GREENWALD: Well, the standard ones - pain, loss of function confirmed by x-ray diagnosis.

DR. BOYAN: Dr. Rudicel.

DR. RUDICEL: I would concur with that. A physical exam going along with the problem, x-rays, and pain.

DR. BOYAN: Dr. Rangaswamy.

DR. RANGASWAMY: I would go along with what has been just said.

DR. BOYAN: Dr. Besser.

DR. BESSER: No additional comment.

DR. BOYAN: Then, we are on to the third question. Should any additional or special instructions be added to the surgical technique for this particular device? We will start with Dr. Greenwald.

DR. GREENWALD: The only concern -- and it was a concern that was brought up by the Food and Drug Administration -- and although I am not really familiar with the inclusion of patient inserts into orthopedic devices, generally, there are precautionary statements made in the

labeling, but I haven't really, in just my experience, come across specific instructions that were made available to the patient concerning the use of the device. Oh, that is Question 4.

DR. BOYAN: That is Question 4. We are not there yet. I think this is in reference to the comment that has been made in several of the reviews that we have heard, that this is a technically demanding device to put in place, and so should there be some instructional information provided to the surgeon to help him or her do it.

DR. GREENWALD: I think that is a question best answered by the hand surgeons that are here today. They have read the instructions. And there are two of them at least.

DR. BOYAN: Let's go to Dr. Rangaswamy.

DR. RANGASWAMY: I think the brochure does give an outline of how to do the procedure, but I wonder if this is something that should be available to people who are going to do it on a videotape or something, that they would understand, and plus they would also need to know some caveats as to where they could get into trouble and how they would avoid getting into trouble, because there is not a lot of room to get into trouble there.

DR. BOYAN: Do you have anything you want to add,

Dr. Nelson?

DR. DAVID NELSON: No.

DR. BOYAN: Are there any other comments? Dr. Skinner.

DR. SKINNER: This is the type of procedure that is going to be done primarily by a surgeon once a year, twice a year type of thing, and based on that, just as in total knee replacement, there ought to be very specific surgeon brochures to help the surgeon do the best job possible to prevent the learning curve problem.

DR. BOYAN: Thank you. Dr. Nelson.

DR. DAVID NELSON: Dr. Skinner, I am not sure that is the case because I think what we will probably find is that there is a very few number of surgeons who choose this particular option, and they are doing a lot more than one or two.

DR. BOYAN: Any other comments? Okay. Now, the fourth question is: Should any specific information be given to patients regarding the device or their surgery, such as limitations in activity or rehabilitation?

I have waiting for this question, so I could have a chance to answer it. I think that absolutely yes, there needs to be more patient information than currently exists, and certainly the patient needs to be made aware of the

negative consequences of a device of this type.

In that light, the fact that no FDA MDR has officially been filed, there is certainly documentation of negative consequences that can occur with this device. In Dr. Braun's paper, at the very least, that paper should be made available to the patients or information from that paper.

Let's go around starting with you, Dr. Nelson.

DR. DAVID NELSON: Can I ask a general informational question before we get to that, because I think it will tell me where I go with the answer to that question.

Are we at this panel in a moment going to vote on this?

DR. BOYAN: No, we are actually going to get a break, and we are going to take 10 minutes to go outside and do whatever people do on breaks, and then we are going to come back and vote.

DR. DAVID NELSON: Okay. So then I have to ask this question. Is it possible at some point, when we vote to either approve or disapprove this, to ask that data be kept in the future, either in the form of a registry or not, either for all of the devices sold or for some percentage of devices sold, and make that part of our approval?

DR. BOYAN: Or part of our motion we don't approve. It would be part of our motion.

DR. DAVID NELSON: Correct. Okay.

DR. WITTEN: You can include that in your recommendation.

DR. DAVID NELSON: Then, I would agree with you that since we do have limited information on this device, that some of the information that we do have from Dr. Braun's papers -- that's obviously where it comes from -- should be available, but I don't think we should give the whole paper, because patients can't understand that, but some of the information contained in that, say, there is a 10 percent failure rate, et cetera, would be appropriate.

DR. BOYAN: Dr. Roger Nelson.

DR. ROGER NELSON: I also agree that I think that we need to give the patient some information, but I think we need to be very aware when we give patient information, that we don't also have an iatrogenic effect, and that we give a list of items and the patient goes down and says, oh, should I have that or should I have that or should I have that.

So I think whenever that is framed, those list of questions or comments, that we be very careful not to make this into an iatrogenic kind of approach. I think there are a number of other items that I think we would like to have

if we can do a post-market kind of surveillance, if you will, of hand function, a standardized kind of hand function perhaps, or a patient satisfaction kind of information, some other information related to the patient, not just related to the device, because the device is implanted in a patient and the patient has a life, and we need to know about that patient's life.

So whether it is a surgical implantation, yes, the surgery was a success, but did the patient ever use it? No. Or that kind of device. So I would advocate for some kind of information that is retrievable, related to the patient and the use and interaction of this device by the patient by some kind of mechanism.

DR. BOYAN: Dr. Silkaitis.

DR. SILKAITIS: Yes. I just want a clarification on the patient information directed towards FDA. In terms of the fact that the patient information would be considered part of labeling, and therefore would undergo FDA review, my comment is will the panel members be involved in the review of that patient information sheet, or would that be an internal process?

DR. WITTEN: I think what we are hoping for is to get enough recommendations about what the panel feels is appropriate or important to include in that patient

information labeling, and take it from there.

DR. BOYAN: Thank you. Dr. Holeman.

DR. HOLEMAN: I certainly think that the patient should have access to all information that is necessary for the patient to make an informed decision, so when that patient decides to go along with the procedure, that patient knows what outcome can be expected.

In that sense, I guess I kind of disagree with Dr. Nelson, should the patient have enough information that he or she chooses not to have the surgery, then, that's okay, too, because then that patient would have made the best decision.

I also would like to add to that, that perhaps Number 3 should be broadened a little bit, inasmuch as we are talking about information, because I don't see where the physician has a lot of information in reference to making a good decision about performing that particular procedure on a patient, and I think that somehow that information should be made available.

When I look at what has been included to go on the labeling, it says that the label cannot provide all of the information necessary, and then my question would be where will that information be necessary, where will be provided, so that the physician can gain access to that information.

DR. BOYAN: Thank you. Dr. Skinner.

DR. SKINNER: I guess I need some information from the FDA. Is the package insert supposed to replace the informed consent process?

DR. BOYAN: Dr. Witten or Mr. Stevens, do you want to address that?

DR. WITTEN: It is not meant to replace the informed consent, but it is an additional way to provide information to the patient.

DR. SKINNER: I think that the information provided to the patient should provide the usual sorts of things that you might find in a drug thing. The incidence of loosening is 10 percent in followup for 1 to 10 years. It may be higher with greater activity levels, that sort of thing, and it should be quite general and not terribly specific, so that a patient can understand it.

DR. WITTEN: I wonder if I could clarify what part of our question is before we finish going around the room, and whether this should go in the surgeon instruction or would be thought of as patient information. I think perhaps it would be both.

But if there is any way that the panel can give us a recommendation when you talk about activity, to characterize the activity postoperatively and in the longer

term, that might be expected or might be a limitation to instruct the patient about.

DR. SKINNER: Part of the process in the informed consent is letting the patient know what is going to happen after they have their arthroplasty, and before the surgeon gets to that process, he has to provide the patient with risks, alternatives, and prognosis.

The alternatives include such things as arthrodesis, which would be something you would tell the patient would be for the working man, the patient that is going to do heavy labor. The patient who is going to get the anchovy operation is going to be someone who is going to be more interested in fine activity perhaps.

Each surgeon has their own take on which patient is the best patient. I don't think I can give very specific suggestions for what should go in the patient information. Along those lines, I think that is up to the surgeon. That is why I asked about the informed consent.

DR. DAVID NELSON: Dr. Skinner, you referred to an anchovy procedure. I am not sure everybody knows what that means.

DR. SKINNER: Well, I haven't done many of these. I am a hip and knee type of guy. But I have done some of these where you take the palmaris longus and you roll it up

in a little ball, and you stick it in that hole where you take out the trapezium.

DR. DAVID NELSON: I think you are just referring to what we have in our documents as any of the variety of ligamentous reconstructive procedures.

DR. BOYAN: Dr. Greenwald.

DR. GREENWALD: I don't have any comment.

DR. BOYAN: Dr. Rudicel.

DR. RUDICEL: I don't have anything further to add.

DR. BOYAN: Dr. Rangaswamy.

DR. RANGASWAMY: I just have one question. This is more for my information. The issue that Dr. Holeman brought up in terms of the surgeon -- and I agree with everybody here that obviously, it has to depend upon the surgeon as to what they tell the patient -- but the question is how does the surgeon, when you market this product and it's available, et cetera, how does the surgeon get hold of the information.

We assume that they will look at the literature, but we all realize that there are some problems with it, and I guess that is one of the questions, whether they are told this kind of data and some of the flaws in the data that are present, at the same time saying that there is an option

that can still be considered because it still appears to be effective.

So that is just a question that I have, and as far as the patient thing is concerned, I think it really does depend upon the surgeon. You can put it all down on a little sheet, like the drug things and stuff, as Dr. Skinner said, and leave it there, but if the surgeon doesn't sit down and explain everything to the patient, I don't think it makes any difference how much you write and put inside.

DR. BOYAN: Dr. Besser.

DR. BESSER: I guess a question to the hand surgeons on the panel. I am correct that you would advise your patients postsurgically as to what activities are and are not advisable for using the reconstructed hand, no handball, no --

DR. RANGASWAMY: Yes.

DR. BOYAN: Let the record reflect that Dr. Rangaswamy agreed with Dr. Besser, the answer was yes.

Mr. Melkerson.

MR. MELKERSON: Just a quick point of clarification on something that comes up over and over again with the FDA. What is the appropriate mechanism to get that to the surgical community, because we have used the package insert as what we believed to be a bit of information that

the surgeons look at, but we are informed by surgeons and the manufacturers that is not where they look for that information. So maybe the panel could give us a little guidance on where they think it would appropriate.

DR. BOYAN: Dr. Skinner.

DR. SKINNER: I have done hundreds of total hips, and I don't think I have ever seen a package insert.

DR. BOYAN: Dr. Holeman.

DR. HOLEMAN: I don't know if it is appropriate to ask a question at this point, but it has to do with the request that prior to scheduling the surgery, there should be documented counseling regarding the contraindication or complication associated with the instrument, with the device. Could you elaborate on that a little bit?

DR. BOYAN: Dr. Holeman is asking one of the surgeons to -- are you asking Ms. Focht or are you asking the surgeon?

DR. HOLEMAN: I am asking Ms. Focht.

DR. BOYAN: Ms. Focht.

MS. FOCHT: We perceive the users of the device to be hand surgeons, and it is our expectation and our experience that the hand surgeons do speak with the patients in great detail about surgical options prior to surgery, and we personally do not collect documented data or evidence of

that for our records.

DR. BOYAN: Dr. David Nelson.

DR. DAVID NELSON: I am a practicing hand surgeon. It is the moral and legal obligation of the hand surgeon to do the informed consent, and the company has nothing to do with it, and it does have to be documented in the chart.

DR. BOYAN: I am going to take the chairman's prerogative to have a last word here, and that is, that I strongly encourage FDA to make the information available both to the patient and the surgeon in some format.

With that, I would like to tell you all that we are going to have a short break. I am an aggressive chairman, 10 minutes. Count them, 10. I will come out and get you.

[Recess.]

DR. BOYAN: The break is over. Back to work.

Before we begin, Mr. Dillard, if you could come back up and just review with us again how this PMA differs from all other PMAs.

MR. DILLARD: I would be happy to. Thank you, Dr. Boyan. This PMA is very different from what you have seen in the past, there is no question, and I understand that that is part of what you are struggling with at this point.

One of the situations that I think you ought to

consider for this PMA is that -- and I think this factors in very well to probably your recommendations and your voting status coming up here -- but there is a couple of things I want you to keep in mind.

One is the definition of valid scientific evidence. Valid scientific evidence that is defined in 21 CFR 860.7, if I can remember it off the top of my head, gives us the regulatory guidance of what is considered to be valid, what is the scientific evidence that we say yes, it is valid and we consider it or can consider it in our decisionmaking process of the approvability or not approvability of a product for its stated intended use, and what you should factor in then, in addition to the definition of valid scientific evidence, is, is the valid scientific evidence plus your deliberations, considerations, and anything else that you have discussed today, whether or not that adequately gives a picture of the risk versus benefits of the product and the safety and effectiveness, and keep in mind that what you are thinking about is does the valid scientific evidence presented provide reasonable assurance of safety and effectiveness for the product for its intended use.

I think if you keep that in your mind, I think that is going to help you in your deliberations, your future

deliberations today and tomorrow, too, and about any motions you might make.

Again, to this type of product, it is different and I don't want to rehash how it is different. I mean I think you all have done a very nice job discussing it. And the data here is what is different. The data from a retrospective point of view as opposed to a prospective point of view is what you are considering. I think that is where your uneasiness is, is that you are very used to in this setting looking at the prospective data set.

But I think again, if you consider it keeping in mind valid scientific evidence, safety and effectiveness, and reasonable assurance of that safety and effectiveness, you will have the right framework as you are trying to discuss the product.

I don't know if that is getting to the differences. I don't want to go into too much detail about the differences again, because there are differences. The hodgepodge that we discussed of data can go all the way down to significant clinical human experience with a legally market product, and that still defines valid scientific evidence.

DR. BOYAN: Thank you very much. Yes, Dr. Skinner.

DR. SKINNER: Could I ask Mr. Dillard something here? What are we doing here in terms of setting a precedent for future devices, anything at all in terms of this 515(b) PMA process?

MR. DILLARD: In terms of precedence, this is the first time -- it is not the first time that a 515(b) PMA has gone to panel, and the one that immediately comes to mind that is not necessarily a good example, but it is one that had multiple panel meetings, are the breast implants, and they did go to a couple of panel meetings with differing recommendations over that time frame, and so from the standpoint of setting a precedence, there have been other 515(b) PMA devices that have been voted on.

There have been other 515(b) PMAs that have been looked at from the same standpoint that you are looking at this PMA here today. So in terms of precedence, I think what we are trying to do, and I think what we are trying to do in the Agency, is allow the flexibility and the opportunity for you as the experts in the field, who have used this type of product, who are familiar with the type of procedures that we are talking about, give you the opportunity to discuss and bring to the forefront clinical experience, your look and read of the data that is being presented, that in this case is literature information, and

to try to put some reasonableness on that data set.

So this is something that while precedence is something that is a word that could be used for this, it also is what I would term more to be a pilot situation of what we are trying to do at the Agency. We are trying to give that opportunity to people other than just FDA, air some of these issues in an open public forum just like this, and so from that standpoint, it is a little bit newer than what we commonly do in advisory committee meetings.

DR. BOYAN: Thank you. Yes, Dr. David Nelson.

DR. DAVID NELSON: Just to followup on Dr. Skinner's point, though, despite what you have just said, could not someone come back later and say wait a second, you can't do such and such now because of that panel before?

MR. DILLARD: I think I would -- and I am getting a little bit different focus here -- I think that for this product, you are saying the data here says something to you, whatever it says. Whether or not that precedence can be extrapolated to other products, to other situations, is something that is very individual for the PMA and very individual for the situation.

I think in terms of setting a precedent, these are all individual, there are not very many of them. There probably won't be that many in the future that come to a

panel under this circumstance, so they already are rare cases.

I don't think you are setting a precedent no matter which way you go, saying that all other PMAs have to be at a certain level, whether novel or 515(b) Class III preamendments products. I think you will be voting on the level for this product and perhaps subsequent products of this product category, but I think it is exclusive for this product, if that helps.

DR. BOYAN: Thank you.

Could we have a motion made? Dr. Rangaswamy, would you be prepared to make a motion? Wait. I did this too soon.

Ms. Nashman, could you instruct us how to behave?

MS. NASHMAN: Yes, I would love to.

Actually, before I go into reading of the voting options, this is just a request. You all asked if we used the proceeds of these meetings, and we do. One of the ways we do that is by looking at the transcripts. So, unless you speak clearly and concisely into the microphone, and state your name, it will be hard for us to reconstruct the scene later. So if you could do that, I would appreciate it.

Panel Voting

Let me now get into the voting process. Now that

you have finished your discussion, you will be asked to formally vote on a recommendation to FDA on this submission.

I would like note again that this is going to be a recommendation to the FDA. Dr. Boyan will ask for a motion from the panel, and there are going to be three options for panel recommendation to the FDA. These options are as follows.

First, approvable. Second, approvable with conditions. Third, not approvable.

They are described as follows. If the device is approvable, you are saying that the FDA should approve the PMA with no conditions attached. The second option is to recommend that the device be approvable with conditions. If you vote for approvable with conditions, you are attaching specific conditions to your recommendation that FDA approve the PMA. The conditions must be specified when a motion for approvable with conditions is made. In other words, you may not vote for approvable with conditions and then determine the conditions later, or vote for approvable with conditions and then not state conditions.

Examples of conditions or preapproval, conditions are draft labeling and a resolution of questions concerning some or any of the data that has been presented. Examples of postapproval conditions are post-market studies and the

submission of periodic reports.

You should propose the extent of the conditions of approvability, such as the number of patients to be followed and/or the number, interval, and type of report to be considered. In all cases, you must state the reason or purpose for the condition.

The last option is not approvable. The third option, the Act, Section 515(b), Part 2, paragraph (a) through (e) state that a PMA can be denied approval for a number of reasons. I will discuss three relevant reasons.

The first is the lack of showing of reasonable assurance that a device is safe under the conditions of use prescribed, recommended, or suggested in the labeling, and let me further describe this.

Safe means that there is a reasonable assurance that a device is safe when it can be determined safe based upon valid scientific evidence that the probable benefits to help from the use of the device, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks. It is a benefit-to-risk ratio.

The valid scientific evidence used to determine the safety of a device must adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended use and

conditions of use.

A second reason to suggest disapproval is a lack of showing of a reasonable assurance that the device is effective under the conditions of use described, recommended, or suggested in the labeling.

Effectiveness can be defined as the reasonable assurance that a device is effective when it can be determined that it will provide clinically significant results.

This determination must be based upon valid scientific evidence that a significant portion of the target population, the use of the device for its intended use and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Finally, the PMA can be recommended for nonapproval if, based upon a fair evaluation of all the material facts and your discussions, you believe the proposed labeling to be false or misleading.

If you vote for disapproval, the FDA asks that you identify the measures you believe are necessary or the steps that should be taken to place the application in an approvable form. This may include specifics on additional studies.

The process of voting is going to begin with a motion from a member of the panel. It may be for any of the three options - again, recommendation for approvable, approvable with conditions, or not approvable.

If the motion is seconded, the Chair will ask if anyone would like to discuss the motion, and so on. Again, please remember the proceedings are taped for later transcription, nonverbal signals are not captured on tape. If you wish to second, you should state so rather than nodding your head or waving your hand. You may vote yes, no, or abstain.

A majority vote carries the motion, and the voting members for this afternoon's portion of the meeting are as follows: Drs. Besser, Greenwald, David Nelson, Roger Nelson, Rangaswamy, Rudicel, and Skinner. Dr. Boyan, as the chairperson, votes only in the case of a tie.

At this point, I will turn the meeting back over to Dr. Boyan.

DR. BOYAN: Thank you. Before beginning the voting process, I would like to mention for both the panel's benefit and for the record that the votes taken are votes in favor of or votes against the motion made by the panel. These are not votes for or against the product.

Again, I would like a motion, and I would like to

give Dr. Rangaswamy the opportunity to make that motion.

DR. RANGASWAMY: I would raise the motion that the product be approvable with condition.

Should I announce the conditions, too, at this point?

DR. BOYAN: Yes, please.

DR. RANGASWAMY: The conditions should include a clearer definition of the indications as discussed here on the panel, the wording in terms of "painful degenerative arthritis," et cetera. Also, to include the standard clinical evaluations that were also discussed, which is the presence of pain, limited range of motion, x-ray changes, as well as function, and in the insert that is provided, to identify some of the problems, the complications, so that that information is available to the surgeon and to the patient.

The last thing is for some -- and this is a question that I have first before I add it to the motion -- whether one can add the post-market -- I mean it is already marketed, but surveillance of this, say, maybe two or five years from now, probably five years, because the device is really not used that much, and even to pull back some of the older patients to see what really happened to them would be very useful scientific information.

MS. NASHMAN: You can include that within the motion.

DR. RANGASWAMY: Yes, I would like to include that with the motion.

DR. GREENWALD: I will second the motion.

DR. BOYAN: The motion was seconded by Seth Greenwald. Is there any discussion of the motion? Seth.

DR. GREENWALD: I seconded the motion, and I would like to add some -- I don't know if I would call it clarification -- but some facility to what Dr. Rangaswamy has said.

Rather than use the horrific term "post-market surveillance," it is already marketed, I would like to suggest that perhaps a registry be included as part of the company's future efforts to track what is certainly a limited number of devices. I mean if only 480 have been implanted to date, certainly, that should not produce an overriding burden on the part of the corporation to at least keep track of who receives these, as the number is likely to be small.

Secondly, I took very much to heart Dr. Skinner's commentary, and have known this for many, many years, that surgeons slimly or scarcely read the package inserts that are accompanying these devices, and perhaps vis-a-vis Mark

Melkerson, perhaps there could be another way of encouraging the company, with FDA encouragement, to include some of the packaging labeling concerns, limitations, and contraindications in a surgical technique which is surely to be published by the company for distribution to surgeon users.

Lastly, I think Dr. Holeman made a good comment about the utilization of patient information, and this is one of FDA's concerns, and I think some thought should be given on the part of the company, and again encouraged by FDA, to provide some sort of patient information aside from the packaging insert that the patient is likely to see.

DR. BOYAN: Are you offering those further comments as like in effect amendments to the motion?

DR. GREENWALD: Well, I think they supplement the amendment she has already made.

Yes, Dr. Roger Nelson.

DR. ROGER NELSON: Again, in the area of supplement or clarification of the surveillance issue, the registry kind of issue, I would like to encourage, so that we don't come into the same problem four or five years from now, is that when these devices are examined, that the company or the mechanism of the surveillance include pre-post kind of study where we are using standardized

valid, reliable measures of hand function, a standardized form of patient satisfaction, a standardized form of a reliable, valid health-related quality of life kind of measure, that would be appropriate for a patient that has had hand surgery, if they do exist.

I imagine that there are some forms of standardized hand evaluation that are available. I know that there are standardized patient satisfaction. I believe the OT Association, doesn't the American Occupational Therapy Association -- well, I would like for them at least to look at some of these issues of having a standardized evaluation. Otherwise, we are going to come up with soup again in terms of trying to figure out what we have.

DR. BOYAN: Yes, Dr. Rudicel.

DR. RUDICEL: I could just comment on that. I think that is opening sort of a second can of worms that this panel could not deal with today. The Outcomes Committee in Orthopedics has been dealing with that quite extensively, and for the last three or four years, have been developing those types of questionnaires, which are not yet fully validated and standardized, but they are in the testing phase, the hand instrument being the furthest along, but I think probably within the year, that will be available, and I think that is something to be considered in

the future, but would be difficult right now.

DR. BOYAN: I would like to just keep us on the motion, because we are each going to get a chance to have one last comment as to why we voted the way we voted, after we get to vote. So is this comment going to be on the motion? I am going to try to repeat the motion that I think we now have in a second.

DR. DAVID NELSON: Go ahead. Just do the motion.

DR. WITTEN: Excuse me. If Dr. Nelson had a comment about assessments, I think it might be useful for us to hear it.

DR. DAVID NELSON: I would like to address that because I totally agree with my namesake, Dr. Nelson, as well as Dr. Rudicel, that it would be great to include all of that, and it doesn't exist, so we can't include it.

However, I do agree with the thrust of what you are saying, is we don't want to be here in five years if we have, say, some sort of registry, and not have any data. So, I don't know what the mechanism is that will give us some good data, but that is something that is highly desirable, and I think it is doable.

DR. BOYAN: Dr. Skinner.

DR. SKINNER: I think we have to be very careful with mandating these sorts of things. This is a prosthesis

that is only put in a few times a year apparently in San Diego. It is put in limited areas probably around the rest of the country, and mandating a surgeon to obtain that data mandates that the company provide money to get the surgeon to get that data.

I think we should probably stop at the registry, mandating only obtaining a current address for each of the patients, something on that order, so that they can be examined at a later date if need be.

It also raises IRB issues when you start mandating all these things and whether you can even sell the prosthesis.

DR. BOYAN: Would you allow me, as a restate the motion, to leave some of those decisions up to staff, FDA staff? I think they are aware of what is reasonable and what isn't reasonable.

DR. SKINNER: Good.

DR. BOYAN: Here it is. The motion that currently is on the floor is approval with conditions, and those conditions include that there be a clear statement of the indications for use, and that they be related to standard clinical indications for therapy of this kind; that there be an insert that identifies complications both for the surgeon and for the patient, and that FDA and the company consider

mechanisms for getting the information to the surgeon for how best to use the device in some sort of technical training instrument that they will actually read and use; that there be some kind of post-market surveillance developed and that that be left up to staff to work out, but that we recognize that given the actual number of patients that actually receive this device, that it be rational and reasonable, whatever the post-market surveillance is.

Have I covered everything that we need to cover?

DR. GREENWALD: Dr. Boyan, I would feel much more comfortable if you avoided the use of post-market surveillance and use the word registry.

DR. BOYAN: Registry is fine with me. Okay. So strike the term "post-market surveillance" and use the term "registry" of patients receiving this device.

So that is the motion on the floor. Since the motion has been moved and seconded, then, let's bring it to a vote. Will all those in favor of the motion, raise their hand.

[Show of hands.]

DR. BOYAN: We are going to have to go around the room. Okay. Hands down.

Let's start with you, Dr. Skinner. Are you in favor, against, or abstain?

DR. SKINNER: My hand is up in favor.

DR. GREENWALD: I am in favor.

DR. RUDICEL: I am in favor.

DR. RANGASWAMY: I am in favor.

DR. BESSER: I abstain.

DR. DAVID NELSON: I am in favor.

DR. ROGER NELSON: I am in favor.

DR. BOYAN: And Dr. Silkaitis and Dr. Holeman cannot vote.

All right. The motion carried. We have no votes against the motion. We have one abstention.

Now, the recommendation of the panel, then, is that the premarket approval for the Avanta Braun-Cutter Trapezio-Metacarpal Prosthesis be recommended with conditions as described.

I would like to turn this over to our executive secretary.

MS. NASHMAN: I guess we are about to adjourn for the afternoon. It has gone rather quickly. I would like to remind panel members to please take all of your confidential material with you. We have been having some problems with the locks on the door.

DR. BOYAN: Wait one second. Don't we need to have opportunity to explain are there any issues --

DR. WITTEN: I think they need to explain why. We need to go around the room and everyone state why they were in favor or against.

DR. BOYAN: That is exactly what I was trying to state.

Dr. Skinner, would you like to state why you were in favor of the motion?

DR. SKINNER: I felt that the evidence provided was valid scientific evidence to support a recommendation for approval with conditions.

DR. BOYAN: Dr. Greenwald.

DR. GREENWALD: I too believe that given the minimal indicated use vis-a-vis the number of these devices, that the evidence presented, although rather singular, was in fact reasonably convincing, and I believe that to deny surgeons and their patients the opportunity to utilize these devices for the indications indicated would be a wrong.

DR. BOYAN: Dr. Rudicel.

DR. RUDICEL: I think the material presented shows that the device is safe. I think we had minimal data showing its effectiveness, and adding the proviso to the acceptance, I think will allow us to continue to show its effectiveness.

DR. BOYAN: Dr. Rangaswamy.

DR. RANGASWAMY: I would probably say the same thing that Dr. Greenwald said.

DR. BOYAN: Dr. Besser.

DR. BESSER: I will agree with Dr. Rudicel just to be different. I think that the device has been shown to be safe. I haven't seen evidence to show that it is effective, and I am not sure whether the registry will be thorough enough, I guess, to gather that data, but again, I saw no reason to deny surgeons the opportunity to use this device should they choose. Therefore, I abstained.

DR. BOYAN: Thank you. Dr. David Nelson.

DR. DAVID NELSON: Well, I think given the definition of legitimate scientific evidence by Mr. Dillard, we did have that evidence that it was reasonably safe and reasonably effective, not scientifically safe and effective, it is not that level, but it is reasonably safe, reasonable effective, and I agree with Dr. Greenwald that I think it would be inappropriate to deny this prosthesis to those surgeons who feel they understand it and want to use it based on their surgical judgments closed to other options, and would be inappropriate to deny it also to their patients.

DR. ROGER NELSON: I agree with Dr. David Nelson in terms of all of the items, so nothing additional to add.

DR. BOYAN: I want to thank the panel and remind everybody that we are to absolutely remember that this is confidential material that we have carried into the room, and Ms. Nashman is going to tell us what to do with our material.

MS. NASHMAN: Just take it up to your rooms this evening, please. Tomorrow, we will destroy it.

DR. BOYAN: Do I have a motion to adjourn?

DR. ROGER NELSON: So moved.

DR. BOYAN: Second?

DR. SILKAITIS: Second.

DR. BOYAN: We are adjourned.

[Whereupon, at 2:55 p.m., the meeting was adjourned, to reconvene on Tuesday, June 10, 1997.]